Journal

OF THE UNIVERSITY OF TORONTO

MEDICAL SOCIETY

NOVEMBER 1963 VOLUME XLI NUMBER 1

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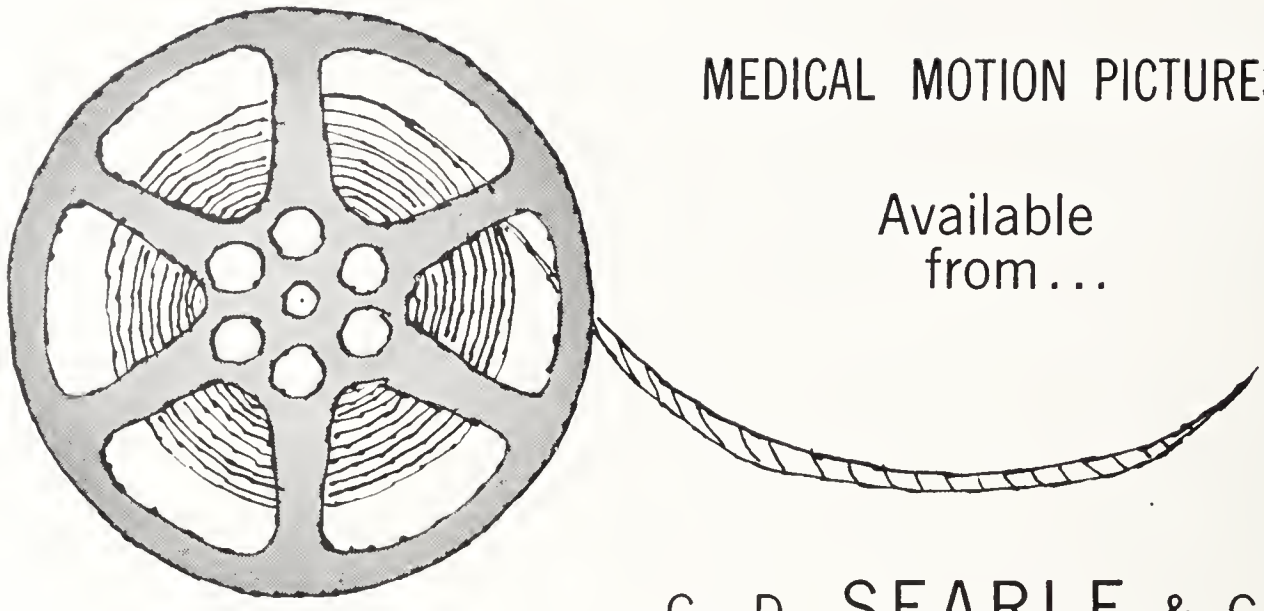

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Editorials

"It is difficult to ascertain to what extent a gentleman should be instructed in medicine before he can pretend to practice . . ."

Any system of medical education must parallel and be molded to the rapid advances in medical science and practice. That this precept has been recognized is given evidence by the surge of concern over the selection of medical students and recent improvements in the medical and premedical courses.

The success of a medical school in producing graduates of high standards is necessarily limited by its weakest link—its students. We have been accustomed to select applicants largely on the basis of their senior matriculation or science arts standings. Because it is recognized that the students who will ultimately be most successful do not necessarily score highest in these criteria, and because it is certain that personality types, social adaptability, and other extra-academic factors play some role in an applicants success, some American medical schools employ a consideration of the following five points in the selection of their students: the results of the Medical College Admissions Test (MCAT), premedical academic record, faculty recommendations, extracurricular activities, and personal interviews. The justification of any method of selection must rest upon the correlation between the results of applicant testing and applicant performances in medical school. Although there is a gross relationship between MCAT scores and student success, its value in predicting the acadamic outcome of any individual student is minimal. The problem of student selection is still unsolved.

To what extent and in what subjects should a premedical student be instructed in. The astounding advances in medical sciences make it imperative that the aspiring doctor have a sound knowledge of the various chemistries, physics, biology, genetics, and biostatistics. To practise medicine intelligently demands that the prospective student be conversant with these basic science principles. To practice medicine as a responsible member of a thinking society demands that the student have an appreciative understanding of the various humanities, national and international affairs. The time available in any premedical course is too limited to fulfill both these ideals. One attempt at solving this dilemma is in practice at Boston, Stanford, and Johns Hopkins universities, where the medical student may pursue an intergrated course in the humanities and medicine, graduating as a Bachelor of Arts and as a Doctor of Medicine.

The traditional "block" system of medical education stood our forefathers in good stead. The subjects of anatomy, chemistry, physiology, and pathology were presented in departmentalized fashion during the preclinical years, followed by the clinical years of bedside teaching. This system reflected the era that gave it birth. It was mechanical and organized, it mimicked the "scientific' approach to things that characterised the times, and it faithfully mirrored the traditional lecture system of the English and Continental schools.

The "block" system is still the basis of medical education to-day. It has, in theory, the advantages of defining what subjects lie ahead, and of assuring an adequate coverage of all the basic medical sciences. Its disadvantages are manifest. It tends to allow each department unnatural autonomy and an approximately equal period of time to present both a foundation, and a survey of recent progress, in each basic science. Advances in biochemistry, genetics, pathology, and physiology far outstrip those of the other sciences, yet the time allotted each department and the details taught are not commensurate with this.

The "block" system turns its students into scribes, lecture hours necessarily increasing in order to present a comprehensive coverage of each course. "The student has little or no choice in the arrangement of his educational programme; little free time is provided, and electives are minimal. He is being taught rather than being encouraged to learn for himself. His relation to the faculty is that of a pupil to his teachers, rather than that of a junior colleague working with those who are more senior."

EDITORIALS

"The traditional curriculum is lacking in stimulation. While the student is busy accummulating facts and preparing to reissue them in whatever form a multiple-choice examination may demand, he is not developing the attitudes of scientific observation and deduction that should be a fundamental part of a doctor's armamentarium."

Many schools have attempted to alter the traditional curriculum, hoping to engender motivation and a selective course of study suited to the individual's interests. At Johns Hopkins the school year has been lengthened, electives are offered, and some students may take courses in the humanities as they take their medical training.

A radically new approach to the teaching of the basic sciences is in effect at Western Reserve. Here there is an interdisciplinary committee which divides the course into three phases, the first concerned with the normal biology of man, the second with the pathologic physiology and the principles of medicine, and the third with clinical medicine and the principles of patient care. Such a system approaches medicine in terms of body units, the nervous system for example, being studied in terms of normal biology in phase one, altered physiology in phase two, and clinical medicine in phase three. At Western Reserve the student, under supervision, begins seeing patients shortly after entering medical school, with an attempt to the intergrate the system with patient observation. Seminars replace many lecture hours and student planned experiments replace the drab laboratory models presently used to illustrate basic science principles.

At present there is virtually no place, nor any credit given, for student research in the orthodox medical curriculum. Albert Einstein School of Medicine, Western Reserve, and Stanford universities offer the interested student laboratory space, guidance and equipment to carry out work in the various medical sciences. Student motivation is increased, and useful principles of scientific methodology are thereby learned.

Many new concepts in medical education are presently being considered and employed in an attempt to keep medical learning apace with the rapid advances in medical science. This editorial is ended in the hope that these efforts will fulfill the aspirations of an old medical educator whose words ushered in this discussion, and now ushers it out into the thoughts of students and teachers; . . . . " . . . . to distinguish between genuine and pretended facts, and amidst the load of learned rubbish with which medicine is encumbered, to select what is truly useful."

W.J.W.

RESEARCH

Research teaches the student to think for himself, to question concepts, and to interpret them in an intelligent way. It teaches him the relationship between the hypothesis and the proof, about success and failure. It teaches him an independence, a boldness to advance his thoughts, yet a modesty to evaluate them critically. This is why the "Student Research" issue is the most important of the year—in no other issue is the contribution of the writer so fundamental, yet so great. Representing months of work, the articles encompass a broad field—from the hypothalamus to the erythrocyte.

At this time I would like to take this opportunity to thank the contributors to this journal and all those who helped in the many facets of publication.

To continue in the tradition of the 1962-63 season, there will be three Parke Davis prizes—one to a member of 4th year, another to a member of 3rd year, and a third to a student in any other year at the faculty. The best of these articles will receive the Academy of Medicine's annual Webster Prize. The winners will be announced at the forthcoming Staff-Student Smoker.

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Etiology of Schizophrenia: Search and Research

W. Weston 6T4

*"Where there is ignorance theories abound"**

Schizophrenia is an enigma—the cause or causes are unknown, it cannot be defined satisfactorily, and it has been denounced as a wastebasket category embracing many illnesses. Equally enigmatic is that one percent of the population is labelled schizophrenic. Struck down in their most productive years of life they occupy one quarter of all the hospital beds in nearly every country. "From some points of view it is the biggest single problem in the whole of medicine" and demands the careful consideration of all students of the health sciences.

The Nosological Problem: What Is Schizophrenia?

Bleuler devised the term schizophrenia from the Greek "schizo"—to split and "phren"—mind to denote a splitting of different psychic functions. One group of ideas, or "complexes", dominate the personality at one time with the "split-off" portions gaining ascendancy at another time. As a result, the schizophrenic's actions and conversation appear odd or even bizarre. There is also a "split" between ideation and affect so that feelings do not correspond to the patients apparent thoughts. He may laugh or cry inappropriately or exhibit no feelings at all. The patient tends to be suspicious, aloof and apathetic and commonly withdraws into a fantasy life which he may embelish with delusions and hallucinations. Catatonic manifestations range from a stuporous condition resembling coma to catatonic excitement in which the patient literally climbs the walls.

Schizophrenia may manifest itself in so many varied forms that one wonders whether he is dealing with a single disease or a group of disease. Szasz has recently argued that the term schizophrenia is a panchreston i.e. an "explain-all", a word that explains everything and therefore nothing. An analagous situation existed in 19th century physics when a mass of confusing data was explained away by the ether theory. "The 'problem of schizophrenia' which many consider to be the core-problem of psychiatry today may be truly akin to the 'problem of the ether'. To put it simply: there is no such problem."[1] If Szasz is correct the term schizophrenia is more correctly used to refer, not to an entity, but to a cluster of similar patterns of abnormal behavior. Research in the past has been hampered by assuming that we are dealing with a biological entity. "Little progress could be made with chest disease when TB, pneumonia and influenza—let alone all the now recognized sub-types of these disease—were lumped together. Only when the correct entities have been hacked out from an unorganized universe of experience can a mature science develop. . . . At present, the clinical diagnosis of mental illness, including schizophrenia and its divisions into subtypes is little past the alchemist stage."[2]

The Historical Background

"It is only a sign of our infantile dependence on authority when we tolerate the existence of rigidly dogmatic schools."—Sargent and Slater[3]

Attempts to explain schizophrenia can be divided into six schools of thought. Each group has its own distinctive methodology vocabulary and doctrine. To the others the methods of each are unfamiliar, the language strange and the concepts esoteric.

1. Biochemical explanation originated with Hippocrates who believed that changes in the blood and the humours of the brain accounted for certain psychological aberrations. The serious study of schizophrenia began in 1896 with Kraepelin who differentiated dementia praecox from manic depressive psychosis which at that time were lumped together under the label "biogenic psychoses". He believed dementia praecox to be an organic disease and, for example, that auditory hallucinations were the result of an irritation of the temporal lobes.

2. Alzheimer, in 1904, attributed schizophrenia to a pathological lesion in the brain. After Noguchi, in 1911, demonstrated that GPI was caused by Treponema pallidum the "schizococcus" was pursued with vigour. The tuberculous origin of schizophrenia was demonstrated by several investigators before the high incidence of tuberculosis among schizophrenics was shown to be a result of hospital life rather than the cause of their disease.

3. In 1911, Bleuler introduced the term schizophrenia

---

*Leucippus

and stressed the importance of psychological factors in the understanding of schiz. Prior to Bleuler's time it was generally accepted that all mental symptoms were caused by underlying physical disorders. At about the same time Freud was developing his psychoanalytic interpretations of mental illness and Jung applied these concepts to the psychogenesis of schiz.

4. The genetic theory of schiz. developed in Germany when social heirarchy and inferior races were popular concepts. Most studies designed to demonstrate the hereditary nature of schizophrenia failed to separate genetic from environmental influence—the parents who supply the genetic material also provide the environment. Recent studies with identical twins have stimulated considerable interest.

5. Harry Stack Sullivan, in 1947, emphasized the social environment as an important etiological factor. Since then epidemiological studies have linked social class and social isolation with the incidence of schiz.

6. Adolf Meyer presented his Psychobiological viewpoint in a symposium on dementia praecox at a meeting of the British Medical Association in Toronto in 1906. A mental disorder is not a "disease" visited upon a person from without but the abnormal reaction patterns of a person of a particular genetic endowment and life experience to the stresses of his life. According to Meyer, schiz. can be the end result of many different causes.

At the present time these schools have tended to polarize around two opposing viewpoints. At one pole are those who maintain that schiz. is an organic disease citing genetic, biochemical and neuropathological studies as their evidence. At the other pole are those who insist that schiz. is a psychogenic disorder. They are not impressed with the evidence of organicity and quote psychological, sociological and psychoanalytic studies to prove their point. In general, the organic position is advocated by investigators most familiar with the basic medical sciences and the European traditions in medicine; the psychogenic position, by those most familiar with the behavioral sciences and U.S. traditions. One of the causes of this bifurcation of opinions is the doctrine of specific etiologies which states that a disease can be adequately explained in terms of a single cause. Views such as Manfred Bleuler's that schiz. is the result of an incompatibility of personal and environmental demands sound suspiciously like the ancient Chinese notion of an upset of the proper balance between the yin and the yang. The modern researcher thinks in terms of specific single cause and neat biological explanations, and hence a cure, at the expense of broader research. "In reality however, search for *the* cause may be a hopeless pursuit because most diseases are the indirect outcome of a constellation of circumstances rather than the direct result of single determinant factors."[4]

In 1958, after an extensive review of the recent literature on schiz., Bellak[5] suggested the "Multiple-Factor" hypothesis of schiz. which states that schiz. is a syndrome manifest as a severe disturbance of the ego brought about by a number of chemogenic histogenic, genogenic, or psychogenic factors in various combinations. Meyer-Gross warns of the danger inherent in the multidimensional approach of not seeing the forest for the trees.

The Genetic Hypothesis

There is no doubt that schizophrenia runs in families but it has been extremely difficult to sort out the relative influence of nature and nurture. Kallmann has shown that the individual's average expectancy of developing schizophrenia varies directly with the closeness of his blood relationship to a schizophrenic patient —"a conclusive proof of the operation of heredity."[6] About one-quarter of identical twins have been found to develop schizophrenia in the absence of similar environments while close to one-half of fraternal twins remain discordant despite similar environments.

Relationship To A Schizophrenic	Incidence Of Schizophrenia (%) (from Kallmann)
None	0.8
Half-sibling	7.1
Sibling	14.3
Fraternal twin	16.4
Identical twin	86.2
Child of one schizophrenic parent	16.4
Child of two schizophrenic parents	68.1

Pastore, in a critical review of Kallmann's earlier work, found so many weaknesses in the argument that he concluded, "the genetics of schizophrenia is still an open question."[7] On the other hand, Hurst criticized Pastore for ignoring the vast body of Kallmann's evidence.

Identical twins have more in common than their genetic endowment. For example, in some primitive cultures identical twins were supposed to be the same human being miraculously doubled. They were given the same name and treated as a single person. Many twins seem to experience difficulty distinguishing "I" from "Thou" and folie a deux has been commonly observed in which the two partners develop shared delusions and symptoms and become mentally ill at about

the same time. Until the present there have been too few studies of schizophrenia in identical twins separated at birth and reared in different families to evaluate the relative importance of genetic and environmental factors.

The exact mode of inheritance, if any, is even less certain. Kallmann stated that schizophrenia was probably due to a mutant recessive gene which might be responsible for a specific type of enzyme deficiency. Koller argued that an incidence of schizophrenia among children which exceeds that found among siblings supports the theory of dominant transmission. Slater suggested that schizophrenia is the result of the action of a "great number of genes of small effect."

Supposed constitutional differences in schizophrenics have been used to support the genetic hypothesis. Kretschmer stated that schizophrenics tend to be of asthenic (slender) physique and recently Sheldon confirmed his findings indicating that about two-thirds of schizophrenic patients have an asthenic build. However, schizophrenia occurs among a young age group which tends to be more slender than the average population and the withdrawn introverted nature of schizophrenics would not be conducive to muscular development. Recently the fingerprints of 100 carefully selected schizophrenics were compared with a control group of 50,000.[8] The findings were an increased frequency of a few special patterns suggesting a constitutional defect.

Few investigators believe that schizophrenia is inherited directly but hold rather that it is transmitted in the form of a predisposition that requires psychogenic stress for its precipitation.

Biochemical Studies

"Behind every crooked thought there lies a crooked molecule." Ralph W. Gerard.

When modern science denied the duality of mind and body the concept of a purely mental or wholly physical disease became untenable. All diseases are psychosomatic because man is an indivisible body-mind unit. Within this framework the psychiatrist must postulate that all thought is related to rearrangements of molecules and hence that there are neurobiochemical correlates of mental illness. In his search for the crooked molecules, the biochemist has examined every tissue and organ in the schizophrenic. Many biochemical abnormalities were later discovered to be the result of dietary insufficiency or idiosyncracy secondary to hospital life. One group of workers found certain abnormalities in the thyroids of schizophrenics, a consequence of a dietary deficiency of iodine which was corrected by order-

ing iodized salt for the hospital kitchen. The widely acclaimed Akerfeldt test was considered diagnostic of schizophrenia but was soon found to be secondary to a deficiency of ascorbic acid. "Year after year, papers appear which purport to distinguish between the state of schizophrenia and that of normalcy. The sum total of the differences reported would make the schizophrenic a sorry physical specimen indeed: his liver, brain, kidney, and circulatory functions are impaired; he is deficient in practically every vitamin; his hormones are out of balance, and his enzymes are askew. Fortunately, many of these claims of metabolic abnormalities are forgotten in time with a minimum of polemic, but it seems that each new generation of biologists has to be indoctrinated—or disillusioned—without benefit of the experience of its predecessors."[9]

The studies of periodic catatonia by Gjessing[10] and others are probably the only biochemical studies thus far which can be accepted almost without reservation as significant. In two percent of schizophrenics, there are phasic variations in the total nitrogen balance associated with periodic mental changes. When the patient is treated with thyroxin and a low protein diet to stabilize his nitrogen balance, the periodic psychosis is abolished. But the maxima and minima of the curves for nitrogen retention and mental state do not necessarily correspond and it is not fully understood what the relationship is between nitrogen balance and periodic catatonia.

Hallucinogenic drugs including LSD, mescaline, adrenochrome and bufotenine have in common the ability to produce vivid symptoms such as hallucinations, feelings of unreality, paranoid reactions and loosening of association without also producing disorientation. This similarity between drug induced psychoses and schizo-

phrenia led many to argue by analogy that schizophrenia is caused by a toxin. Hoffer and Osmond[11] in Saskatchewan have shown that adrenochrome, a deteriorated form of adrenaline ("pink adrenaline") produces a temporary psychosis. They postulated that the metabolism of adrenaline is abnormal in schizophrenics. Under stress, an excess of adrenaline is produced and converted to adrenochrome which in turn causes the psychotic reaction. Many investigators have failed to find adrenochrome in the bodies of schizophrenics and have labelled adrenochrome psychosis a laboratory artifact. The similarity between the experimental psychoses and schizophrenia is at best superficial and these drug induced states are more akin to toxic psychoses than to schizophrenia. Also the fact that repeated daily doses of these drugs induces rapid tolerance casts doubt on the hypothesis that they play a central role.

Since 1956, Kety, chief of the Laboratory of Clinical Science of the National Institutes of Health, has conducted a carefully controlled program of biological research in schizophrena designed to minimize some of the common errors of previous research. One ward houses fourteen "clearly diagnosed" schizophrenics maintained under standard conditions of diet and hygiene and psychiatric and nursing care.

Another ward houses a control group of "normals" living under similar conditions. Several of his findings contradict results of earlier, less carefully performed, research. For example, he has found a normal rate of glucose and oxygen consumption and cerebral circulation. In conclusion he states, "Our schizophrenic patients, individually or as a group, have shown little abnormality in the biological studies which have thus far been completed." [12]

Psychological Studies

The bulk of recent research in the etiology of schizophrenia has been on an organic, metabolic discoveries and biochemical techniques, while psychological research has had relatively few "new" methods available. However, Jackson, after a survey of the recent literature on schizophrenia, states that in the U.S. a psychological explanation is currently favoured.[13] All too often psychological theories have been both unproven and unprovable, confirming Oscar Wilde's statement: "Nowadays to be intelligible is to be found out." However, psychology has benefitted from several series of impressive observations which have at least an indirect bearing on schizophrenia.

The Family Environment

Studies of the early mothering process and examination of the schizophrenic's family milieu suggest the importance of psychological factors in the etiology of schizophrenia.

Ribble[14] made clinical observations on 600 infants for a long period of time noting withdrawal or regressive behaviour, negativism or any exaggerated reaction to changes in routine or other frustrations. All these items were observed against the background of the long-term development of the infant-mother relationship. About 30% of the 600 babies showed a generalized muscle tension which disappeared when the baby sucked or was in close contact with the mother. Tension was also relieved by stroking, petting or cuddling. Children deprived of these elements of mothering showed a persistent muscular tension accompanied by irregular breathing with instability of circulation, digestion and excretion. "Mother-bankrupt" babies also showed severe psychologic symptomatology. Negativism was manifest by the infant's refusal to suck, generalized rigidity of the body, resistance to imposed movements, screaming, breath holding and constipation. A severe form of regression occured in which the baby appeared to function the way it did prior to birth — the sucking reflex disappeared, muscle tone was lost and the child lay motionless in a stuporous condition. After five years of continual observation Ribble was convinced that the symbiotic relationship of mother and newborn child was as basic and necessary to the child as food and water, and as fundamental to his emotional and social prosperity.

Spitz studied the effects of maternal deprivation on infants and Bowlby brought together a great mass of data on infants deprived of maternal warmth and mothering in Europe because of war relocations. Both found that children deprived of a mothering figure when less than one year old showed, in their later years, a predictable slowness in psychological development, isolation and tentativeness in their relationships, and a general apathy.

Experiments with animals have been designed to show the effects of social experience in infancy and have been carefully controlled to rule out hereditary factors. Purdue Wistar rats brought up by "emotionally disturbed" mothers, whether the biological mother or a substitute mother, became "emotionally disturbed" themselves as shown by a tendency to huddle in the corner of the test box and defecate frequently.[15]

All these observations support the concept that early psychologic traumata *can be* of etiologic significance in schizophrenia.

Knowing that maternal deprivation can cause abnormalities of behavior, psychologists began to study the families of schizophrenics in a search for specific disturbances in infant-mother relationships. In a study

of childhood schizophrenia, Kanner found that many of the parents were prominent and respected citizens of the community, but that toward their children they were undemonstrative and showed a mechanization of human relationships with an almost complete lack of any real warmth and affection. Lidz and his colleagues studied the families of adult schizophrenics and concluded that, "serious pathology of the family environment is the most consistent finding pertaining to the etiology of schizophrenia." [16] Two-thirds of the families contained one parent who was found to be schizophrenic. Such family groups are unintegrated and are characterized by conflicts between the parents and efforts of each to win the children to their side to obtain emotional support not found in the spouse. The "schizophrenogenic mother" was described as dominating, overprotective but rejecting. The "schizophrenogenic father" is either a passive non-entity or sabotages his wife in her role as mother.

Caught in such family groups, the children are unable to develop healthy patterns of interpersonal behavior. The result is a failure to acquire social skills which produces self-consciousness, insecurity, moodiness and a tendency to withdraw from conflict. In a child's psychosexual development the mother and, to a lesser extent, the father become the models on which the new self is patterned. Brought up in a diseased family milieu a child fails to develop sound personal or sexual identification and he may remain confused about his own identity. The result may be feelings of depersonalization and sexual aberrations.

In an attempt to explain the origins of the schizophrenic's defect in communication, Batson and others[17] suggested the "double bind" hypothesis. The victim of the double bind repeatedly finds himself in situations where he is required to make two quite different and mutually contradictory responses at the same time. His intense emotional dependency on the "binder", who is either parent or spouse, makes it impossible for him to point out or even acknowledge the contradiction yet he can neither ignore nor fail to respond to the paralysing injunction. An example is a high school student who is urged to use initiative in his school work, yet when he attempts to visit the library he is told to stay home in case the parents need him. No matter what he does he cannot win. A variation of the double bind exists where one parent commands a child to do something which the other parent absolutely forbids.

> "In the Eastern religion Zen Buddhism, the goal is to achieve Enlightenment. The Zen Master attempts to bring about enlightenment in his pupil in various ways. One of the things he does is to hold a stick over the pupils head and say fiercely, 'If you say this stick is real, I will strike you with it. If you say this stick is not real, I will strike you with it. If you don't say anything, I will strike you with it.' We feel that the schizophrenic finds himself continually in the same situation as the pupil, but he achieves something like disorientation rather than enlightenment. The Zen pupil might reach up and take the stick away from the Master, who might accept this response, but the schizophrenic has no such choice since with him there is no not caring about the relationship, and his mother's aims and awareness are not like the Master's." [17]

Thus prevented from communicating in a meaningful way even with those closest to him, the schizophrenic remains isolated, unable to achieve a satisfying relationship with anyone. As an adolescent he dates to "prove" that he can gain the attention of others. Marriage becomes a means of proving that he is a man and that he can love. All his actions have an "as-if" quality; he is split from reality. Whether the double bind is characteristic of schizophrenic families or has special features for such families is not known.

Many of these studies lack controls and suffer from the weaknesses inherent in all retrospective studies. They stress the effects of environment to explain facts which might better be explained in terms of inheritance. A critical study by Oltman[18] and others found the incidence of parental deprivation and broken homes to be very similar among schizophrenics and normal controls. Although nothing has been found which is specific for these families, presumptive evidence indicates that a tremendous amount of conflict, tension and anxiety exists and has always existed in these families. Schizophrenia can be described as an individual's attempt to escape from such an intolerable environment into a private world of his own.

Sensory Deprivation

Marked reduction in sensory input produces a schizophrenoid model psychosis characterized by anxiety, restlessness, inability to concentrate, delusions, hallucinations and even panic. Many patients who undergo eye operations with temporary loss of vision experience some form of postoperative confusion — "black-patch delirium". This is aggravated by the reduction of auditory stimuli which occurs at night. The pioneer experiment on sensory deprivation was carried out at McGill University on students who were paid $20 per day to recline on a foam rubber mattress in a small room kept at constant temperature and humidity. They wore plastic goggles over their eyes to transmit a diffuse grey light and earphones to provide a constant auditory environment. Only 18 of 29 subjects remained in the isolation booth 72 hours. 25 reported hallucinations and some subjects had after effects which lasted for days. Another experiment was designed to test the

hypothesis that the absence of sensory stimuli per se is not the crucial variable evoking hallucinations but the absence of meaningful stimulation. A constant repetetive auditory stimulation plus random flashing of a bulb and flashing of coloured Rorschach cards on the wall were provided. One subject after 38 minutes screamed to be let out, tore off his ECG leads, ripped his equipment apart and clawed wildly at the apparatus. Though he looked terrified he denied completely any anxiety or discomfort.

Apparently when the brain stops receiving meaningful stimuli it manufactures its own by a mechanism called projection. An example of this occurs in normal persons during sleep when dreaming takes the piace of external stimuli. Perhaps when the schizophrenic find reality intolerable and shuts himself off from it, he experiences self-induced sensory deprivation which leads to hallucinations and the formation of a delusional system.

Summary

Schizophrenia is a big problem. Tackling it from both organic and psychologic viewpoints has given some insight into the nature of the illness but the etiology remains a mystery. The majority of investigators are convinced that there is a hereditary transmission of a tendency to develop schizophrenia but the nature of the genetic defect is unknown and no specific biochemical abnormalities have been demonstrated except for the small group of periodic catatonics. The importance of environmental factors in the genesis of schizophrenia is widely accepted but there is little agreement concerning their specific nature.

"This decade was one of widening of conceptualizations. Rather than championing a single etiology, workers implicated multiple factors. The level of question asked most frequently has been: 'What has gone wrong within the person and between the person and society that has resulted in a mutually painful state called schizophrenia?' This question begs for a complex answer — much as the question 'What causes a world war?' does — and on this level of investigation we begin the next decade of research in the etiology of schizophrenia." [19]

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Abstract

Bacterial Contamination of Indwelling Intravenous Polyethylene Catheters: M. S. Druskin, P. D. Siegel; J.A.M.A. *185,* No. 12, 966 (1963).

A study was undertaken on a random sampling of hospital patients to determine the degree of contamination of intravenous polyethylene catheters used for long term parenteral therapy.

The insertion of the catheters was not standardized and was carried out by the hospital staff under their routine operating conditions. Removal was done only by the authors in a uniform, aseptic procedure. The distal 1 inch of the catheters were then cultured at 37°C. in tryptose phosphate broth.

The results were as follows: no positive cultures were obtained from catheters in situ for less than 48 hr. After this time 52% of the catheters gave positive cultures and from these were obtained a variety of organisms: staph. albus was the most common organism isolated, occurring on 59% of the positive cultures. Other organisms present were: staph. aureus, proteus mirabilis, pseudomonas aeruginas, Strep. viridans, B. subtilis E. coli, Klebsiella. It is felt by the authors that 48 hr. is the maximum safe time for the catheter to remain in situ.

Experimental Allergic Encephalitis

L. Geiger 6T4

A MODEL OF A DISEASE

Introduction

One of the most frustrating aspects of research is the very real difficulty involved in finding a practical approach to the problem. Medical research emphasizes this difficulty! A popular method of bridging this gap is to use an experimentally produced disease to study clinico-pathologic entities in man. The purpose of this article is to demonstrate the usefulness of such a laboratory disease, and to indicate a few of its limitations.

Demyelinating diseases are ill-understood and yet, they are all too frequently encountered by the neurologist. However, this type of disease process can be considered only indirectly since the brain and spinal column are carefully encased from view until autopsy, at which time pathologic changes are usually far advanced. In addition, the quantity of available material does not adapt itself easily to research processes. To get around this problem, experimental allergic encephalitis (EAE) is being used to aid the investigation of demyelinating conditions. In the following paper, the rationale behind its use (that is a clinico-pathologic description of EAE and its link to demyelination) precedes the discussion of the current research problem. Demyelination.

Since demyelination is a common response of nervous tissue to injury, we must carefully define what is meant by a primary demyelinating disease. The most prominent condition under this category is multiple sclerosis; most pathologists also include diseases such as post-vaccinal encephalomyelitis, Schilder's disease, acute necrotizing leucoencephalomyelitis and others. Animals also suffer from spontaneous forms of demyelinating disease; one example is swayback disease of sheep (2). Human diseases vary considerably in their clinical and pathologic findings, but fulfil the basic requirements for inclusion. As must now be obvious, these criteria are based on pathologic findings. These are sometimes summarized (1) as:

1) destruction of the myelin sheath of nerve fibres.

2) relative sparing of other elements particularly axons and cell bodies.

3) disseminated foci which are perivenous in distribution.

To illustrate, a brief description of the post-mortem findings in multiple sclerosis is in order (1). Initial examination reveals no gross changes in the brain and spinal cord. Cut sections reveal the small discrete pale-grey lesions which stand out distinctly in the grey matter as well as the white. These lesions are most pronounced in the brain stem, spinal cord and cerebral white matter. Microscopically, early lesions are perivenous with numerous microglial cells, macrophages and lymphocytic infiltration. The myelin and oligodendrocytes degenerate, but the nerve cells and axons in affected areas appear healthy. Later proliferation of astrocytes predominates producing a mat of fibrous gliosis, the so-called plaque.

Experimental Allergic Encephalitis

(1) *Definition*

EAE is the term used to describe the clinical and pathologic changes which are seen as a result of the injection of tissue of the normal CNS into a normal animal.

(2) *History*

Shortly after the introduction of Pasteur's antirabic vaccine in 1885, there were reports of neurologic symptoms differing from rabies in patients treated with the vaccine. Early in this century the effects of injection of normal nervous tissue into monkeys were likened to this post-vaccinal reaction in man (3). Since Pasteur's vaccine contained nervous tissue, the connection seemed reasonable.

In 1935 Rivers and Schwentker were able to produce consistently a disseminated encephalitis in monkeys by multiple injections of an aqueous emulsion and an alcohol-ether extract of brain and spinal cord tissue (4). They described the pathology and found it comparable with human demyelinating disease.

The next major advance was made by Morgan (5) and by Kabat (6) et al working separately. They homogenized brain tissue with Freund's adjuvant (an emulsion of a lanolin-like substance, paraffin oil and dry heat-killed tubercle bacilli which had been shown to enhance antibody production to sensitizing antigens). They injected this mixture into monkeys. The incidence and severity of disease was markedly increased. One injection sufficed and symptoms appeared quickly. These developments stimulated a cascade of further research.

(3) *Production of EAE*

The usual technique of producing EAE is to give a single injection of the Freund's adjuvant homogenate of brain tissue by the intradermal route.

After a period varying from ten to sixty days after injection the animal begins to show signs which include weight loss, weakness or paralysis particularly in the hind limbs, convulsions, urinary retention and bowel dysfunction. Death frequently ensues rapidly.

(4) Pathology

At autopsy the gross appearance of the central nervous system is not remarkable; but small petechial lesions may be seen on cut sections (2, 10, 11). They are present in the brain stem, spinal cord, optic nerves, cerebral and cerebellar white matter. Microscopically the foci are related to blood vessels. Early polymorphonuclear infiltration with occasional eosinophils are present with some perivascular haemorrhage. Myelin degeneration is evidenced by paling; however, the axonal preservation is relatively good. Later lymphocytic and other monocytic cells become more prominent with microglial infiltration and proliferation of astrocytes. Sudanophilic products of degeneration appear. After the perivascular reaction has subsided, the residual effects are some fibrillar response and myelin degeneration with relative axonal sparing. The morphologic picture does vary considerably from one species to another but the similarity to the human picture is striking enough to provide a basis for comparison.

(5) *Current Etiologic Theory*

The currently popular etiologic grab-bag in medicine is allergy. Multiple sclerosis now finds itself thrown into this one just as it has at some time been in all the others. EAE, the term used for this experimentally produced disseminated encephalitis expresses in its very name the most prevalent theory as to its basic nature. Indeed, some very suggestive evidence has been accumulated to support the allergic basis of EAE but none is conclusive. Some of this evidence will now be enumerated.

(a) *"Antigen"*: Various attempts have been made to isolate the active encephalogenic agent from CNS tissue. Its physical properties include resistance to heat, ultra-sound, drying and fixation with formalin[4]. It has been shown that myelin-rich fractions are more active than fractions derived from grey matter [5,7]. Roizin and Wechler claim that a mitochondrial fraction is active[9]. Various isolation procedures support the conclusion that the active agent is partially protein and partially lipid[8].

(b) *Nature of the Disease*: Without further explanation, the very nature of the disease mimics a delayed allergic or tuberculin response. There is the initial delay followed by a violent reaction which is enhanced by the addition of Freund's adjuvant.

(c) *Immunologic Tolerance*: This can be induced by frequent small doses of brain emulsion without adjuvant or by treating newborn animals before myelin production is completed[12,13]. The priming dose then has a decreased effect. It is interesting that Kabat et el produced EAE using autologous brain tissue obtained by lobectomy in monkeys.

(d) *Prevention*: Large doses of ACTH and cortisone,[14,15] and 6-mercaptopurine[16] are found to inhibit or retard the development of EAE. Irradiation of the regional lymph nodes near the primary injection decreases the incidence of disease[3]. Total body irradiation enhances its development[26].

(e) *Transfer*: No transfer has been effected by blood cells or serum[6]. However, Paterson claimed that he had transferred disease by lymph node cells[17,18]. Others have failed to reproduce his results. Using parabiosis, Lipton effected transfer in rats[19].

(f) *Antibody Production*:

(i) *Complement Fixation*: This phenomena can be demonstrated in EAE serum to emulsions of rat brain but its presence does not correlate well with disease findings and cannot be related with the etiology of the disease on this evidence[20].

(ii) *Coon's Fluorescent Technique*: Rose et al treated normal spinal cord slices with serum from guinea pigs with EAE and then treated them with an appropriate fluorescent antiglobulin. An increased fluorescence was described which correlated with the position of the myelin sheaths[21,22].

(iii) *In vitro Demyelination*: Recently, Bornstein and Appel obtained interesting results from experiments with tissue cultures[23]. Myelinated newborn rat cerebellum was the source of cultures and these were viewed under high power microscopes. After they were established as healthy cultures EAE serum from affected rabbits was added to their nutrient medium. Controls included sera from normal rabbits and from rabbits which were injected with kidney tissue and Freund's adjuvant.

Demyeliation resulted quickly in cultures treated with EAE serum; the rapidity of its appearance varied directly with the concentration of serum used. First signs showed up as early as one hour

and demyelinating effects were completed in forty-eight to ninety-two hours. These observations were repeated in many cultures. Normal serum and anti-kidney serum had no effect. If the affected sera were removed remyelination in some cases occurred. It was concluded that there was some demyelinating factor present in the serum of the EAE animal.

Another interesting work has been done showing a "gliotoxic" effect of multiple sclerosis serum on tissue cultures of neonatal rat brain.

Present Research Project

Aim: Since there are microscopic changes in the myelin with the addition of EAE serum, there may also be changes in the metabolism of the tissue in vitro, in the presence of the serum. This research project attempts to determine whether EAE serum has any affect on the fatty acid output of rat brain slices.

Method: EAE was produced in guinea pigs and serum taken when symptons developed. Rat brain slices were incubated at thirty-seven degrees centigrade in a physiologic medium. To this medium was added EAE serum or normal serum as control. After incubation a sample of the medium was removed for the determination of free fatty acid.

Results: The addition of serum from diseased rats to the brain slices stimulated the net production of free fatty acids by this tissue.

Discussion: If these results are confirmed, their significant interpretation then becomes the problem. If the same substances in EAE serum causes in vitro demyelination and an increase in fatty acid output of brain slices, it is a logical supposition that the breakdown of myelin is the source of fatty acid. Furthermore, if future experiments show that the activity resides in the 8-globulin fraction, then the theory of antigen-antibody involvement gains support. Although further probing into the nature of EAE itself may justify the pursuit of these experiments, the human application is also significant. Since blood serum is the only requirement for these techniques, they are easily applied to human studies. However, even positive results in such experiments would not prove an allergic basis for multiple sclerosis but would certainly stimulate more research along such lines.

There are many pitfalls in trying to apply the study of experimental demyelination to the human disease. The ground becomes even more shaky when one uses experimental disease to investigate the etiology of the human problems as my research program has implied. As long as the experimenter keeps these facts in mind and avoids poorly supported parallels, the usefulness of laboratory disease will be kept in its place.

Summary

EAE is a useful laboratory condition for the investigation of human disease. Its usefulness as a tool is comparable to that of alloxan, which is used for the experimental production of diabetes in studies of that disease. It makes possible a closer examination of the process of demyelination and may even shed understanding on some of the causative factors involved.

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Abstract

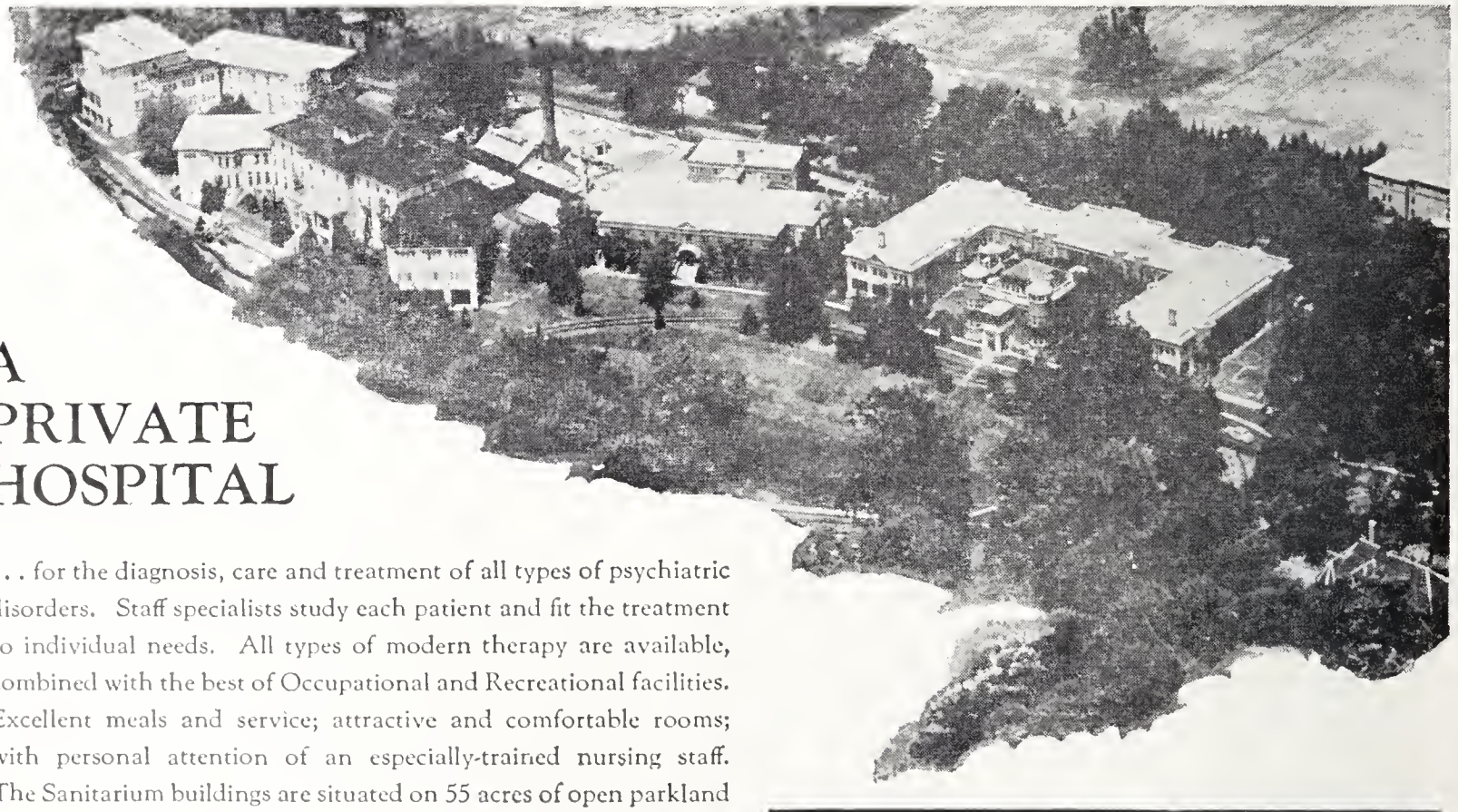
Septic Shock, A. M. Lansing. JCMA. Vol. 89, p. 583, Sept., 1963.

Septic shock is a hypotensive state caused by bacteremia and accompanied by oliguria signifying decreased peripheral circulation. It occurs often after surgical manipulations and contaminated blood transfusions. About two-thirds of cases are caused by Gram-negative organisms.

The mortality is high if a bacteremia progresses to septic shock. Signs of impending shock are shaking chills, malaise, myalgia, high fever with development of full shock within 12 hr. of the first chills. Clinical diagnosis is based on blood pressure, urine output and the shaking chills.

In spite of much experimentation the mechanism of the condition is unknown.

The response to immediate treatment may be quite dramatic. The first step is intravenous infusion and blood culture followed by antibiotic thereapy after identification of the organism. If hypotension is severe or oliguria is present, an intravenous pressor agent is given. Further therapy with hydrocortisone may be necessary.



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The Pathogenesis of the Arthus Phenomenom

*William J. Weiser** 6T4

Introduction

The Arthus phenomenon has served since its original description in 1903[1] as a prototype of an allergic reaction. Understanding the details of this complex lesion serves then as a model for the further investigation of other hypersensitivity states.

When an antigen is injected into a specifically immunized reactive animal a lesion develops at the local site of inoculation. The intensity of this lesion depends partly on the species of animal used, partly on the quality[3] and quantity[4] of circulating antibody in the animal, and partly on the quantity of locally injected antigen. Grossly the reaction may vary in intensity from a mild transient local erythema, to erythema and edema which may be transient or prolonged, to intradermal hemorrhage, necrosis, and solughing of the skin at the site of injection. Microscopically vascular arteriolar spasm has been observed, followed by vasodilatation and a general decrease in vasomotion of the involved vascular bed. Stasis may follow these preliminary vasomotor changes. Polymorphonuclear leukocytes (PMNL's) have been seen to adhere to the affected endothelial walls as early as six minutes after the inception of the lesion[5], and precipitates of antigen-antibody complex accumulate in the lumen of small venules and capillaries as well as intramurally and to a lesser extent perivascularly[5]. With the early accumulation of antigen-antibody precipitates and polymorphonuclear leukocytes, thrombi are seen to occupy many of the finer vessels. These consist of PMNL's, antigen-antibody complexes and platelets. Grossly edema has been found by some workers to be a function of the numbers of PMNL's aggegated at the site of the lesion[6,7]. Serous transudation, fibrinoid changes in the vessel walls, erythrocyte diapedesis, frank hemorrhage and PMNL exudation all may ensue.

During these early changes endothelial alterations have been observed[8], but whether it is just one of a panorama of events somehow initiated by the interaction of antigen and antibody, or whether it is in fact a leading event which precipitates many of the ensuing hemorrhagic and necrotic changes is still undecided.

Mononuclear macrophages, probably largely of histogenous origin, later accumulate at a time when the number of PMNL's is decreasing, and after several weeks foci of plasma cells may be seen throughout the area.

The Conundrum of the Arthus Phenomenon

A number of fundamental questions still remain unanswered concerning the pathogenesis of this lesion.

a) How does the presence locally of antigen and antibody initiate the lesion?

b) Is the initiation largely due to a direct effect of the antigen-antibody complex on the tissues, or is it due to its ability to release phlogistic agents, or is it due to a particulate phenomenon largely independent of chemical mediation?

c) What is the role of vascular tissue in the Arthus phenomenom?

d) What is the role of PMNL's and why do they localize at the site of the lesion?

e) Finally one would like to know the relationship between the chemical and physical structure of the antigen, of the antibody and of the complex, and certain events in this lesion, such as capillary permeability and tissue damage.

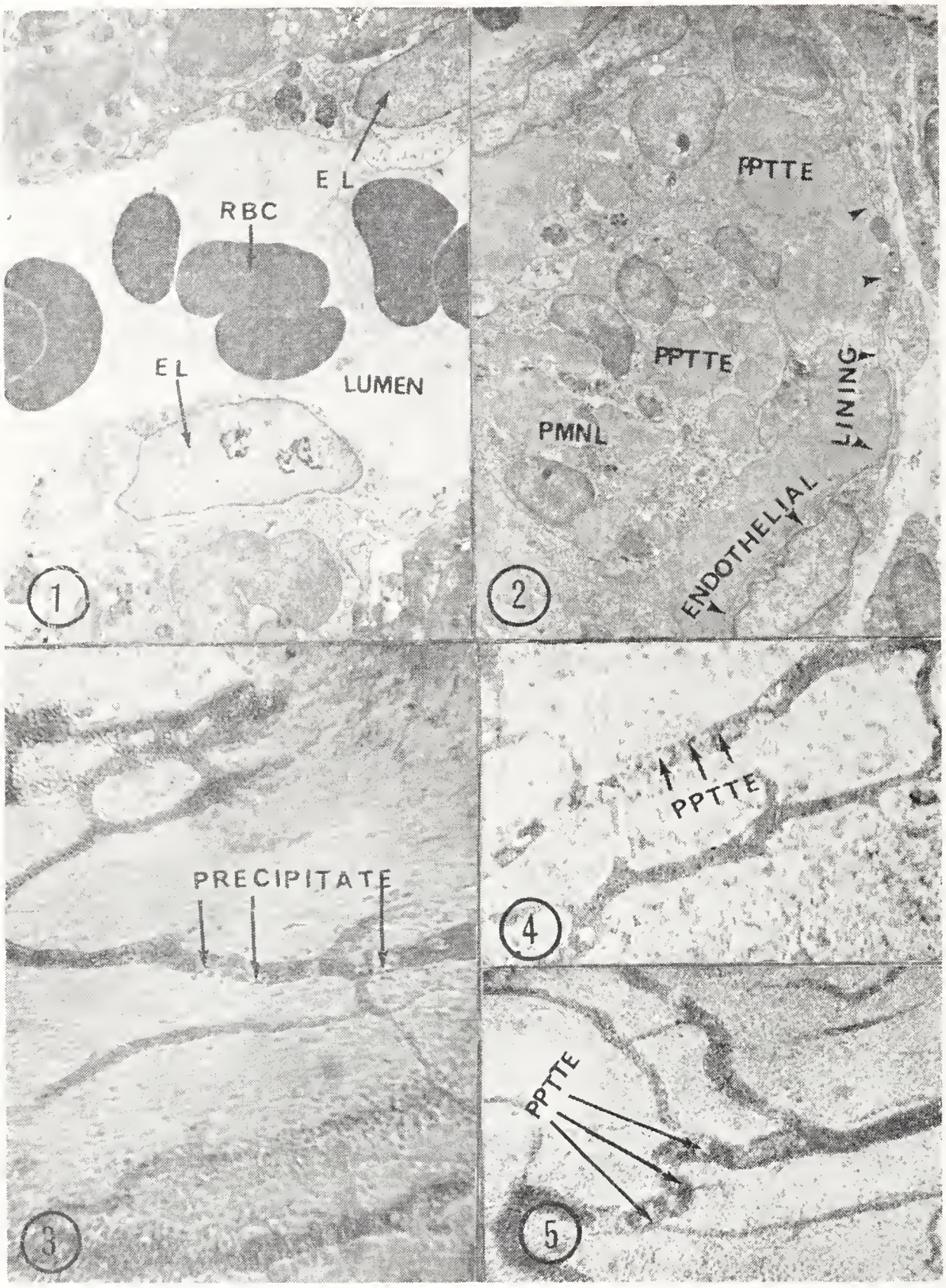
The Pathogenesis of the Arthus Reaction

A) *The Interaction of Antigen and Antibody and the Induction of the Arthus Phenomenon*

Opie[27] hypothesized that the initiation of the Arthus reaction was due to intravascular formation of precipitates· while others[9] have shown that antigen-antibody interaction could result in profound vasomotor changes which may serve to initiate the Arthus phenomenon.

A number of observations have been made concerning the biological properties of antigen-antibody complexes. [2,10,11,12,13] Soluble antigen-antibody complexes are capable of causing smooth muscle contraction, increased capillary permeability, anaphylactic shock in guinea pigs and mice and cutaneous lesions in rabbits, and complexes prepared at equivalence (particulate not soluble) as well as soluble complexes can bind complement and result in the release of 'anaphylatatoxin'[14]. Finally Stephen Boyden[15] has demonstrated the chemotactic property of antigen-antibody complexes on PMNL's, while others[16,17,18]. using in vitro techniques, have produced platelet agglutination and the release of serotonin and histamine by the interaction complexes and platelets.

These effects of antigen-antibody complexes seem to suggest that the local presence of antigen and anti-



Key To Plates.

EL. Endothelial Lining

RBC. Red Blood Cell

PML. Polymorphonuelear Leukoeyte

PPTTE. Preeipitate of Antigen-Antibody Complex

(1). An electron micrograph showing a small vessel lumen in the reverse passive Arthus reaction. Note the relative scareity of precipitate as eompared to plate 2.

(2). An eleetron micrograph showing a small vessel lumen in the active Arthus reaction. Note the abundanee of immune precipitate in the lumen, and in the polymorphonuelear leukocyte situated in the lumen.

(3). A low power light micrograph showing immune preeipitate in the vessels of a transparent ear chamber.

(4) & (5). Low power light mierographs essentially the same as plate (3).

body in complex form either itself or through the rele aseof chemical mediators initiates this form of allergic inflammation.

Although the Arthus phenomenon may be mediated by the release of phlogistic chemical agents dependent on the local interaction of antigen and antibody and tissue or hematogenous components, the exact isolation and identification of these inflammatory intermediates has never been accomplished, although Menkin[91] and others[20] have described chemical mediators of normergic inflammation.

Another possibility in the mode of action of immune complexes is that they are in themselves noxious to all or certain target cells and tissues. The interaction of

antigen, antibody, and complement has been known to be involved in the immune lysis of cells, and in certain types of phagocytosis, yet immune complexes themselves have never been shown to be damaging to other cells or tissues. Although Germuth et al.[21] declared that immune complexes led to an eosinophilia and fragmentation of collagen fibers in the avascular cornea of a rabbit, others[22] have proven using electron microscopy and immunoflouroscopy thae alteration of collagen fibers by immune complex does not occur in the cornea of the rabbit, others[22] have proven using electron microscopy and immunofluoroscopy that alteration of collagen fibers by immune complexes does not occur in the cornea of the rabbit.

B) *The Role of Vascular Tissue in The Arthus Phenomenon*

If the local interaction of antigen and antibody in the Arthus lesion does not result in direct damage or the release of significant inflammatory agents, it could still be injurious if it led to local anoxia. There is no evidence suggesting that immune complexes are oxidative inhibitors, therefore, local anoxia would be dependent on local ischemia. Several workers[8,22] have found that Arthus lesions do not occur in avascular tissues despite the local interaction of antigen and antibody.

C) *The Physico-Chemical Properties of the Antigen and Antibody and the Arthus Lesion*

How then does the coupling of antigen and antibody lead to local ischemia and subsequent hemorrhage and necrosis?

Antibodies that will not form precipitates with their appropriate antigens are designated 'non-precipitating' antibodies. It has been shown that substantial Arthus phenomena cannot be induced by 'non-precipitating' antibodies[23]. Furthermore, recent study has shown[24] that in a variation of the Arthus phenomenon (reverse passive Arthus) in which antigen is injected intravenously and shortly afterwards antibody intradermally, the severity of the lesion is generally less than, and fluorescent and electron microscopic sections show less intravascular precipitate than in the ordinary Arthus reaction (Plates 1 & 2)

All of these observations seem to fit a common scheme, which is that intraluminal accumulation of particulate immune complexes is perhaps a key event in the production of this type of immediate hypersensitive state. The induction of this lesion may depend on the presence in the vessels of immune precipitates formed by the diffusion of soluble antigen away from the site of injection and its interaction with precipitating circulating antibody. 'Non-precipitating' antibodies cannot form intraluminal aggregates, cannot lead to vascular occlusion, and do not produce significant Arthus lesions[23]. If antibody interacts with a relatively greater proportion of antigen, soluble instead of particulate complexes are formed[25]. In the reverse passive Arthus the intravenously injected antigen may be greater enough in quantity than the locally injected antibody so that soluble complexes[25] are largely formed instead of particulate ones, and since vascular blockage cannot occur, ischemic changes do not follow. (plate 1) If antigen interacts with antibody in proportions approaching an excess of antibody, then particulate complexes form[25]. This is the case in the ordinary (active) Arthus lesion, in which the quantity of circulating antibody exceeds that of the locally injected antigen. (plate 2)

D)*The Role of PMNL's in the Progression of the Arthus Lesion*

In the Arthus type of immediate hypersensitivity state, precipitated complexes are seen lining the vascular endothelium, in the endothelial gaps, and entirely occluding tiny vessels. PMNL's and platelets are seen forming mixed thrombi with these precipitates, the PMN's evidently being attracted[15] to phagocytose the complexes (Fig. 2). PMNL's then serve to ingest the foreign immune particles, and form part of the thrombi that at times entirely occlude small vessels. The result of such occlusion could then lead to local tissue anoxia, endothelial alteration, hemorrhage and necrosis. It is reasonable then that in leukopenic rabbits in which few PMNL's can participate in thrombi formation, the precipitate-leukocyte thrombi will be fewer in number, smaller in size, resulting in less vascular occlusion, less ischemia, less endothelial and hydrostatic changes and therefore less edema. Also the absence of leukocytes prolongs the local presence of immune precipitates. A prolongation of a milder reaction may then be expected with the later oncoming histogenous macrophages having the burden of removing the majority of the precipitate.[6,7,24]. This explanation of the role of PMNL's agrees with the work of others[6] who have observed that in leukopenic animals the Arthus phenomenon progresses more slowly, lasts longer, is of less intensity, and that edema is less than in animals with a normal leukocyte count.

E) *Unsolved Aspects of the Arthus Phenomenon*

The most challenging concepts are concerned with the quality or avidity of an antibody and the phlogistic nature of the complex formed with it. Little has been reported in the literature concerning the physical nature of the antigen, the antigen / antibody molecular ratio

in the complex, and the relationship between the time of immunization of an animal and the nature of its circulating antibody, to the production of the Arthus phenomenon.

Whether or not antigen-antibody complexes cause platelet agglutination in vivo is still undecided, as is the role of platelet thrombi in the pathogenesis of this lesion.

All these enigmas must be answered before a full understanding of the Arthus phenomenon can be obtained.

F) *In Vivo Observations*

The technique of construction and observation of the transparent ear chamber has been previously recorded[26]. It was felt that this technique afforded an opportunity to observe the entire sequence of events in the induction of the Arthus phenomenon. It could bridge the gap between serialized knowledge obtained by taking sequential microscopic sections of the lesion, and the dynamic hypothesis now advanced for its pathogenesis. Ear chambers were implanted into two immunized rabbits and when vessel growth was seen to cover a substantial part of the viewing table, concentrated antigen was injected over both tables. A water cooled light source passing through a microscope to a cine camera enabled us to view and film the entire inception of this lesion.

Immediately after the injection of the antigen there was no change in vascular tone, contrary to that observed by others[9]. This may be partly due to a scarcity in our chambers of fully mature arterioles with smooth muscle capable of responding to the immune stimulus. Capillary vasomotion did not seem to be qualitively altered either, except for perhaps a slight prolongation of the capillary pulsations. About eight minutes after the injection, tiny white precipitates were noticed inside capillary lumina. At first these tiny particles were carried away as emboli, but later larger aggregates formed and adhered to the endothelial lining. Platelets and leukocytes were seen to permanently adhere to the endothelial wall, some larger vessels being reduced to capillary dimensions by this leukocytic pavementing. Leukocytes were seen to form occlusive thrombi with precipitates and probably platelets and as this occurred stasis developed. Frequently blood flowed at one end while the other end of a vessel was static. By 15 minutes after injection significant stasis had occurred with homogenized red blood cells intermixed with occluding thrombi occupying the vascular bed. Twenty-four hours later hemorrhage was observed in one of the chambers.

It was observed that the quantity of the precipitate was the major factor initiating complete stasis. When a small quantity of antigen was injected into the chamber, precipitates were slow to form and those that formed were small and were rapidly carried away by the blood stream as immune emboli, and stasis never developed.

Summary

A dynamic view of the pathogenesis of the Arthus phenomenon has been presented. The successful, yet still incomplete use of the transparent ear chamber has tended to substantiate our belief that immune precipitates gathering in the lunina of local blood vessels and the ensuing leukocytes and platelets that adhere to the precipitate and to the damaged endothelium form occlusive thrombi which initiate stasis in the involved vessels and produce a local area of ischemia and subsequent necrosis.

ACKNOWLEDGEMENTS

The successful application of this work would never have occurred without the support and encouragement of Dr. H. Z. Movat. I wish also to thank G. Helmel 6T6, and B. Pearson 6T6 for technical aid, lacking which none of the ear chamber work could have been done. Lastly my gratitude to Gunther Thomas for his assistance in all the phases of photography employed.

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Abstracts

Immunization with Live Measles Virus Vaccine: H. R. Brodie; J. C. M. A. Vol. 89, Sept. 1963, p. 533.

One hundred and fifty children who were at least eight months old, had no measurable serum measles-blocking antibody and who had no previous immune globulin injections were vaccinated with an attenuated Edmonston strain measles virus. They were observed for fourteen days by their parents for cough, rash, conjunctivitis and their axillary temperature recorded.

During the fourteen days, the children appeared to develop a mild case of measles which, however, lasted only three to four days and had no complications. Eight weeks after vaccination blood studies showed circulating measles-blocking antibody. Subsequently, 21% of the children were exposed to naturally-occurring measles and did not develop the disease.

In spite of its apparent effectiveness, widespread acceptance of the vaccine will probably depend on parental education and amelioration of some of the measles-like side effects.

Placenta Accreta: H. Brody; J.C.M.A. Vol. 89, Sept. 1963, p. 499.

Placenta accreta is a condition in which there is no line of cleavage between placenta and myometrium because of an absence of the decidual layer. It is quite rare but is also an emergency condition when encountered. The "classical" patient is a multipara, about thirty years old with a history of uterine trauma or congenital abnormality who enters labor two to four weeks before term.

After delivery the placenta fails to separate and intrauterine manual examination reveals no line of cleavage between placenta and myometrium. At this point further examination is deferred until an adequate supply of blood is available. When this is so, intrauterine examination is carried out to determine whether placenta accreta is present and if so, is complete, partial or focal.

If total placenta accreta is present, removal of the placenta should not be attempted; the cord should be tied short and the patient placed on broad-spectrum antibiotics. Hysterectomy should be done only in the case of uncontrolled hemorrhage or pelvic phlebitis.

Should the placenta accreta be partial, as much as possible should be removed manually. With an adequate blood supply available and the patient receiving an oxytocic and antibiotics, careful observation should be maintained at least 24 hours. If hemorrhage occurs, a hysterectomy must be done.

Studies of Urinary Tract Infections in Infancy & Childhood: J. Winberg, et. al. British Medical Journal, Aug. 31, 1963, p. 524.

Using a hemagglutination technique the investigators studied the antibody responses of 20 patients and 25 controls to acute and chronic urinary tract infections with a view to specificity of response and aid in diagnosis of the infection and its anatomical location. They were particularly interested in the antibody responses to coliform bacteria.

The results indicated that in acute infections in which the concentrating ability of the kidney is unimpaired (e.g. cystitis) there was no rise in antibody titer. However, in infections with impaired concentrating capacity (e.g. pyelonephritis) there was a marked antibody response and a tendency for the infection to terminate spontaneously. This difference in response may be used as a diagnostic tool in determining whether renal parenchymal involvement has occurred. Finally, increased antibody titers were found in chronic asymptomatic bacteriuria and pyuria suggesting parenchymal damage.

Further studies are planned to determine the value of antibody response as an aid in differentiating between diseases distal to and within the renal parenchyma.

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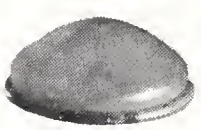

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The Hypothalamus and Anterior Pituitary

K. H. Shumak 6T5

The In Vitro *Relationship Between The Hypothalamus & Anterior Pituitary Gland As Studied By Fatty Acid Mobilization From Epididymal Fat Pad.*

Introduction

It is generally accepted that the function of the nervous and endocrine systems is to exert a co-ordinating and controlling activity on body functions. A major problem in physiological research has therefore been, the manner in which these two systems interact. The two logical sites, anatomically, are the adrenal cortico-medullary junction, and the hypothalamic-hypophysial axis. The latter alternative seems more likely for a number of reasons. The hypothalamus is high up in the central nervous system, in contrast to the more peripheral adrenal medulla. The anterior pituitary gland seems to be the chief regulator of the thyroid, the gonads, and the adrenal cortex, itself, and is therefore, in a sense the master endocrine gland. Finally, hypothalamus and pituitary are linked by a portal system of vessels, and a nerve fibre tract. Considerable work has, therefore, been done, in an effort to elucidate the relationship between pituitary and hypothalamus.

A number of methods have been developed to extract and purify a corticotrophin-releasing factor (CRF) from the hypothalamus. [1,2,3] This CRF has been shown to liberate corticotrophin (ACTH) from anterior pituitary glands incubated *in vitro!* In addition, ACTH is released from the anterior pituitary, in combined tissue culture with hypothalamus, for a longer time than anterior pituitary tissue alone.[4] This data suggests that ACTH secretion by the anterior pituitary gland, depends at least in part, on the hypothalamus.

The posterior pituitary gland has also been shown to influence anterior pituitary ACTH secretion. *In vitro* experiments have demonstrated that a neurohypophysial factor tends to increase the ACTH output by the incubated anterior pituitary tissue.[5] In fact, earlier this year, Schally and Guillemin published data indicating a successful extraction of B-CRF from the posterior pituitary gland.[6]

The work cited thus far has been in reference to ACTH secretion, but similar work has, and is being done, on the anterior pituitary secretion of its other hormones. For example the output of prolactin by the anterior pituitary *in vitro,* has been shown to be decreased when in combined culture with the hypothalamus,[7] suggesting that hypothalamic control of the anterior pituitary may involve inhibition as well as stimulation of hormonal secretion.

A rough scheme representing the interrelating factors may be constructed:

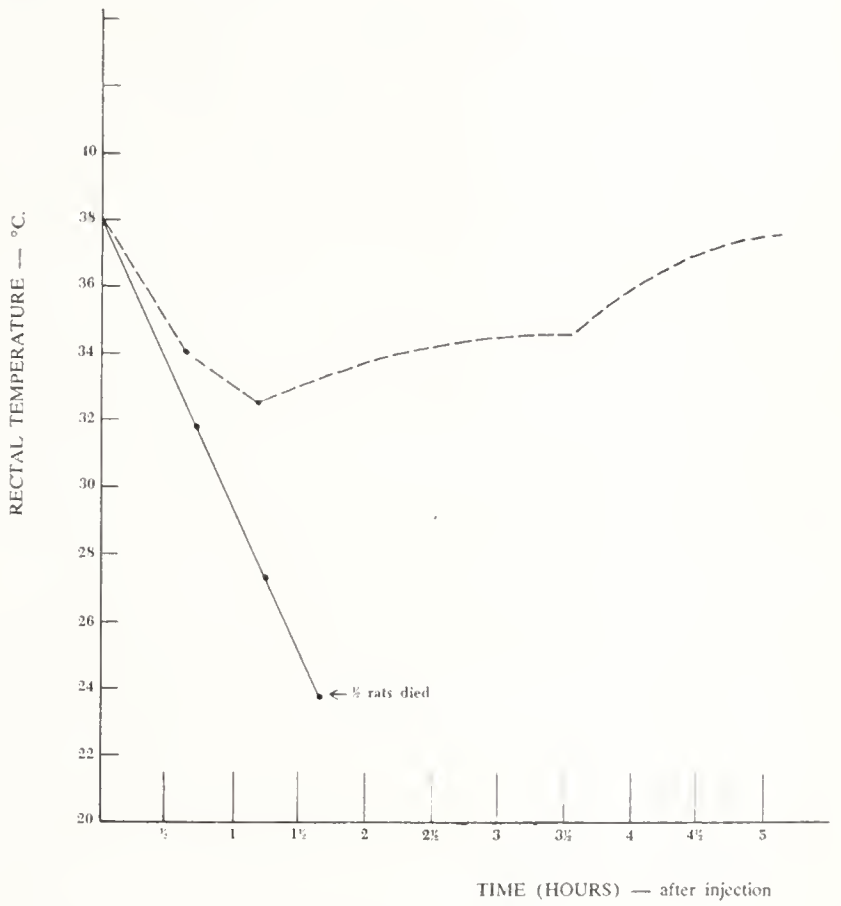

Fig. 1 Effect of Methocarbamol at 2°C.
——— Non-acclimated animals
— — — Cold-acclimated animals

Much more work must be done before the details of such a scheme can be expressed with confidence.

Experimental Work

In the past two summers, work has been done involving *in vitro* incubation of the anterior pituitary gland and the hypothalamus. Our prime interest has been the effect of hypothalamus on the gland, and for this reason, we required a means of assaying the gland's hormonal secretion. Measurement of output of all the pituitary hormones would have been very difficult, and indeed, unnecessary. Rather, it was decided that free fatty acid mobilization from adipose tissue would be used, since it has been repeatedly shown that the anterior pituitary contains and releases fat-mobilizing fac-

tors. [8,9,10] Fat mobilization is a property of not only such established pituitary hormones as ACTH[11] and growth hormone,[12] but, in fact, is also the property which characterizes the fraction H, isolated recently by Rudman et. al.[13] Therefore, it was concluded that release of fat-mobilizing activity was a relatively good index of overall pituitary funtion.

Our preliminary work consisted of incubation of rat anterior pituitary gland halves, and subsequent use of the incubation medium for incubation of adipose tissue. The adipose tissue was obtained by quartering rat epididymal fat pads, and the free fatty acid, released by them into the medium, was measured by microtitration according to the method developed by Dole and Meinertz in 1960.[14] We found that in order to obtain a dose-response relationship between anterior pituitary fat-mobilizing factor and free fatty acid release from adipose tissue, it was necessary to make sizeable dilutions of the gland incubation medium. It was essential to work in such a dose-response range in order that small differences in pituitary output would become evident.

Other variables were also studied, for their effect on regularity of response, including the duration of gland incubation, and the composition of the gland incubation medium. From this basic work, we were able to adopt a standard system for gland incubation, which gave us results with a relatively low standard deviation.

We were now in a position to begin assessing the release of fat-mobilizing activity from the gland under various conditions. Anterior pituitary glands were taken from the following types of donor rats: normal fed, normal fasted, adrenalectomized fed, adrenalectomized fasted, alloxan-diabetic maintained on insulin, and alloxen-diabetic deprived of insulin. The fat-mobilizing activity released by each gland type under the standard incubation conditions was assayed, as was the activity remaining in the normal and adrenalectomized glands, after the incubation. It was found that for each parameter, two relatively distinct groups emerged. During the incubation, a higher amount of fat-mobilizing activity was released from glands of normal fed, normal fast, and alloxan-diabetic (deprived of insulin) donors, than from the other three gland types tested. After the incubation, greater fat-mobilizing activity was found in the two types of adrenalectomized glands, than in the two types of normal glands. The two most important points gained from this data are:

(1) Deprivation of insulin to diabetic rats causes an increased release of fat-mobilizing activity from the incubated gland in comparison with glands from insulin-maintained donors. This may be a factor in the *in vivo* rise in plasma free fatty acids seen in uncontrolled diabetes.[15]

(2) Adrenalectomy causes a considerable increase in total fat-mobilizing activity contained in the anterior pituitary, but at the same time, depresses the amount released during gland incubation.

We have just begun our investigations into the effect of hypothalamus added to the gland incubation medium. Using normal fed and normal fasted rats for donors, the fat-mobilizing activity released by the anterior pituitary glands has been measured for the following incubation combinations:

(1) normal fed gland and normal fed hypothalamus

(2) normal fed gland and normal fast hypothalamus

(3) normal fast gland and normal fed hypothalamus

(4) normal fast gland and normal fast hypothalamus

It was found that each combination yielded the same or less release of fat-mobilizing activity as the gland incubated itself, except for combination (4). This seems to indicate that fasting causes specific changes in both the hypothalamus and anterior pituitary which result in an increased secretion of fat-mobilizing activity. This corresponds with the increased serum free fatty acids seen *in vivo* with fasting.[16]

By the end of next summer, we hope to have extended our studies to include the effect of hypothalamus, from all the donor states previously mentioned, acting on the various gland types. In addition, we hope to have completed investigations on the effects of glucose, insulin, glucose + insulin, adrenocorticoids, adrenaline, histamine, and posterior pituitary extracts on:

(1) Anterior pituitary gland release of fat-mobilizing activity.

(2) Hypothalamic release of factors stimulating the gland's release of this fat-mobilizing activity.

Once we have obtained this data, we hope to publish our results (late 1964), and perhaps add a few more details of the interaction between hypothalamus and pituitary gland.

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(cont. on page 28)

Medical Horizons

Frank Lipson, a fourth year medical student spent two weeks last summer as a guest of the Russian government. Here he writes of his impression of medical education in the U.S.S.R.

The Russian student's medical education begins upon successful completion of highschool which is equivalent to second year university in Canada. The students, generally 18 or 19 years of age, write special examinations in order to enter the medical faculty. About 1/10th of those applying to the medical schools are accepted. This is based on political affiliations, parents economic position, and marks from the previous two examinations, the medical boards preferring students from poor families and party members. The education is free; in fact, the students receive a weekly stipend for their expenses including free room and board. They attend school 11 months of the year with one month vacation.

Medical school is divided into a preclinical course of three years and a clinical course of four years. In the preclinical course they study the basic medical sciences — anatomy, physiology, biochemistry, histology, pathology etc., and in the clinical years they study surgery, medicine, pediatrics, obstetrics and gynecology and specialties. The student spends almost one year on each specialty and rotates from hospital to hospital, each hospital having only one specialty. The professors do not have their own private practice but work solely in hospital. In the morning the professors take the students on rounds and in the afternoon they lecture or else do research. The students have very close contact with professors, and are given a wide and free choice of the material that they wish to study. Their clinical courses are not well defined, nor do the lecturers follow the text books closely, but rather they extract material from the journals and report on the latest papers. Most of the students follow at least one or two journals on the subjects that they feel they will specialize in later. They go to class or rounds from 8 o'clock in the morning until two in the afternoon and then they are free to study or do research work in a project of their choice. The professor who is doing the research assigns the student a part of his research program and only the responsibility of the student determines the limitations of the work. The student receives acknowledgement for the research on publication.

Most Russian students can speak English and were quite interested in the research we were doing in Canada and the United States, but they had much difficulty in understanding where we get our research funds. They wanted an explanation for the "Thalidomide Crisis" for they claimed that this tragedy could not have happened with government supervision as they have in Russia. They were unable to understand how patients could afford proper medical treatment with the cost of medicine and doctors so high, and also wondered where basic research could obtain funds if no capital profit were made.

65% of the Russian medical students are females, who claim fervently that they are more compassionate as doctors with a better understanding of human character, and therefore are able to treat patients more sympathetically. The students live in co-op residences with no supervision, for the dean believes they are mature enough to take care of themselves (no curfews are enforced).

The students write two examinations throughout medical school — one at the end of the preclinical years and one at the end of the clinical years. After graduation the students must serve three years either in the armed forces or in an outpost far from the main cities. After this compulsory duty, they can go into specialization or general practice, which is decided for them by a central staff who know of all available resident positions. At this point it is advantageous to be a member of the party. But the board can do as it sees fit, and as yet no one has been sent off to Siberia.

Frank Lipson 6T4

Abstract

Result of Thalamotomy for Parkinson's Disease: T. G. Speakman; J.C.M.A. Vol. 89, No. 13, p. 652, (1963).

Various surgical procedures for the alleviation of Parkinson's disease have been practised and the author suggests thalamotomy as another possible procedure.

The procedure consists of destruction of the ventrolateral nucleus by an inserted wire loop. The patient remains conscious during the operation and is observed closely for side effects. Indications for the operation include parkinsonism in which the main disability is due to tremor, ineffective medical therapy and no secondary disease. Independent observations one week and two months postoperatively indicated that 81% of the patients were moderately or greatly improved. Other manifestations of parkinsonism e.g. dysphasia, dysarthria were not relieved by the operation and, in a few cases, there was a tendency for recurrence in spite of bilateral thalamotomies.

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The Muscle Biopsy in Duchenne Muscular Dystrophy

C. D. Bell 6T4

Though the histology and altered physiology of all the muscular dystrophies, save that of myotonic dystrophy, are similar, yet these diseases are sharply distinguished from each other by their selective incidence in a population, and by the particular pattern of their clinical course.

Excluding myotonic dystrophy, the three commonest dystrophies seen are[1]

(A) Duchenne (Pseudohypertrophic or Childhood) Muscular Dystrophy

(B) Fascioscapulohumeral (Landouzy - Dejerine) Muscular Dystrophy

(C) Limb Girdle Muscular Dystrophy
  (i) upper limb girdle affected (Erb)
  (ii) lower limb girdle affected (Leyden-Möbius)

Rarer types of dystrophy occasionally seen are Gower's Distal Muscular Dystrophy and Progressive Opthalmoplegic Muscular Dystrophy.

The type of dystrophy discussed in this paper is the Duchenne Dystrophy, which is the most common type seen, with an incidence of approximately in 1:5000 as determined by Soltan[2] in Ontario.

The onset of clinical symptoms is usually between one to five years of age. The patients are almost exclusively males, although a few female cases have been described. A large percentage of cases are found to have a positive family history of the disease with a sex-linked pattern of inheritance [3,4]. The gene responsible for the dystophic trait is postulated to have a high mutation rate. [2,3]

The proximal muscles of the lower limbs and trunk are affected early, the onset of weakness forcing the patient to "climb up his knees" in arising from the prone position (a classical test of trunk muscle weakness).

Muscular pseudohypertrophy is a common feature of this disease though not necessarily limited to it. Classicaly, the calf muscles appear swollen and hypertrophied giving a "Herculean" appearance to the child, although hypertrophy can instead show in the deltoids or buttocks. The disease is progressive with increasing muscular weakness affecting more muscle groups and leading to invalidism, flexion deformities of joints, and death from intercurrent infection at 12 to 20 years of age.

The pathological features of many types of muscular dystrophy have long been known and used in the diagnosis of cases of dystrophy and are a baseline for further research into the nature of this disease. The initial step in a pathology assessment of any muscle biopsy is a rough estimate of the size of the individual fibres, the degree of variation of fibre size, and the distributions of fibres of different sizes throughout the section. If the fibres are distributed as bundles of small fibres amongst areas of large or normal sized fibres, the muscle was either taken from a premature child with yet developing fasicles, or from a child suffering a neurogenic illness. If the fibres are of uniform size, or of varying size, the site of action of the muscle disabling disease is on the muscle fibres primarily, and may be a dystrophy, a myositis, a toxic myopathy, or a collagen disease type of myopathy. Various other abnormalities in size and distribution of muscle fibres are used as diagnostic tools but are not as characteristic of any one condition as in the neurogenic lesion.

Hypertrophy of fibres and variation of size distribution is very common in muscular dystrophy (all types) but is occasionally seen in other types of myositis. A distinction between a myositis and a dystrophy can be made by finding cellular infiltrates (often lymphocytic or inflammatory) in myositis, and by the relative absence of such in dystrophy. However, foci of degenerating muscle in dystrophy may be accompanied by an inflammatory reaction.

Histological differentiation between the various myopathies is difficult and a quantitative estimate of various altered histological features must be attempted. Pearce[5] has stated that myotonic dystrophy reveals more frequent central nuclei and nuclear rowing than this occasional finding in the various non-myotonic dystrophies. Numerous other features found in muscular dystrophy have been described as fibre splitting, small regenerating basophilic fibres, hyaline degeneration, proliferation of sarcolemmal nuclei, fatty and fibrous infiltration of the fasicles, and ringbands. These features are not always found in cases of muscular dystrophy nor are they restricted only to that disease.

Attempts have been made to effect a quantitative assessment of the Duchenne dystrophy pathology and relate it to the clinical picture and course of the disease. In the most part some degree of correlation between the severity of the pathological lesion and the disability of the patient and his future course (checked by retrospect) could be drawn. However these studies[6] only yielded conclusions that patients more severely disabled by muscular dystrophy tended to have more obvious pathology in their muscle biopsies. Histological differentiation between the various dystrophies (excluding myotonic dystrophy) is difficult and these must be separated solely on clinical grounds.

Most of the quantitative assessments of the pathological indices of dystrophy have depended upon the observer's training and judgement in deciding the relative prominence and weight of any specific feature within a slide. The slide was then usually graded as o, +, ++ or +++. This method can show a considerable correlation of pathology to clinical features, and may give consistent results with two separate observers who have had intensive pathological training. However, to the relatively inexperienced many, it does not offer any concrete or objective statement as to prominence of any certain feature, nor is it finely ordered enough to be plotted as a changing parameter through time. The survey being described forewith was undertaken in the hope of establishing the dynamic nature of Duchenne muscular dystrophy, and of determining the relationships of the various pathological features seen on biopsy to the stage of the disease and to each other at succeeding points in time.

As fibre hypertrophy and variation in size is so dominant in descriptions of Duchenne muscular dystrophy, and as expressions of both fibre diameter and variation of diameter sizes are easily attainable and expressable in precise numerical units, a determined effort was made to obtain the standard deviation and mean fibre diameter for 138 muscle biopsies preformed on 134 Duchenne muscular dystrophy patients of varying ages at the Hospital for Sick Children over the past 14 years. These patients were clinically of the classical Duchenne type (except for two girls) and the initial pathological diagnosis of the biopsy confirmed the clinical diagnosis. An extremely small number of patients (not included in the 138) were diagnosed clinically as Duchenne but had a typical or non-diagnostic biopsies. The measurements and computations were plotted against age at biopsy and will be compared with various other pathological features to be assessed at a later date. A series of normal control specimens are in the process of being collected from biopsy or autopsy specimens with no history or signs of neuromuscular disease. The data from these specimens are

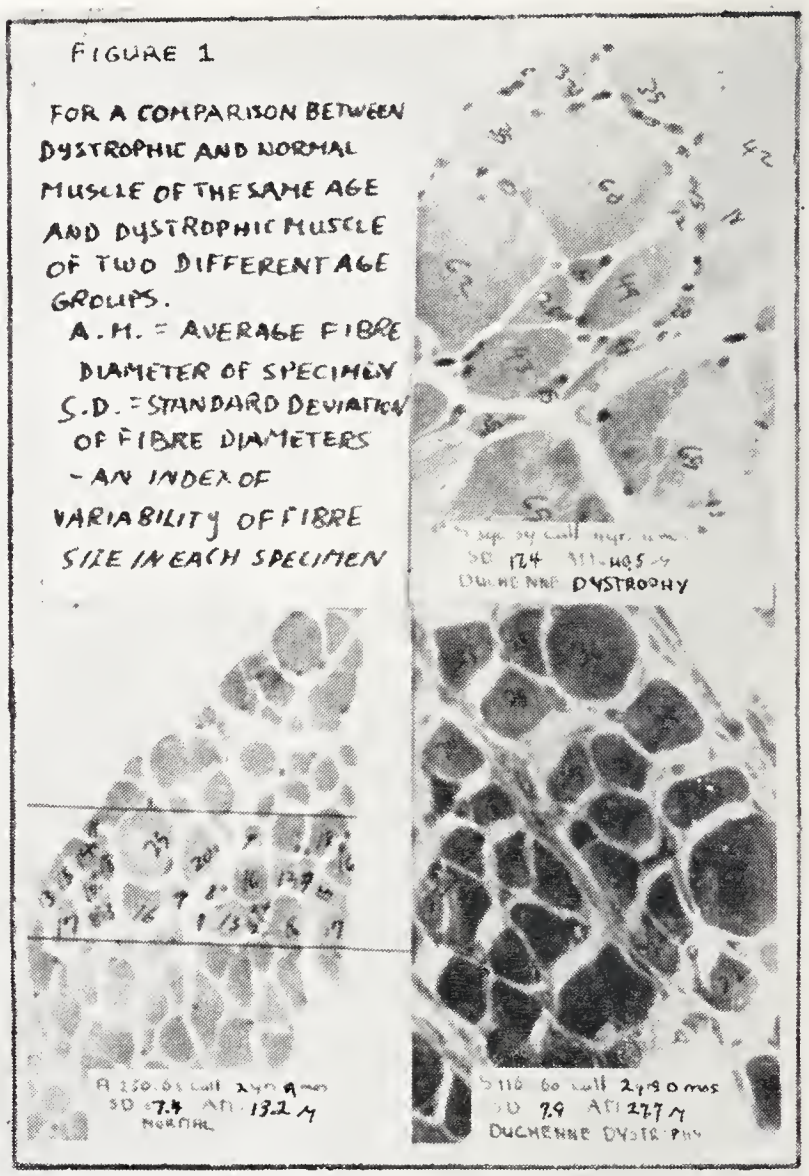
FIGURE 1
FOR A COMPARISON BETWEEN DYSTROPHIC AND NORMAL MUSCLE OF THE SAME AGE AND DYSTROPHIC MUSCLE OF TWO DIFFERENT AGE GROUPS.
A.M. = AVERAGE FIBRE DIAMETER OF SPECIMEN
S.D. = STANDARD DEVIATION OF FIBRE DIAMETERS - AN INDEX OF VARIABILITY OF FIBRE SIZE IN EACH SPECIMEN
DUCHENNE DYSTROPHY

being treated in a similar way as that from the Duchenne cases, and will eventually be compared with the latter, The process of obtaining suitable numbers of control specimens is a slow one, and as yet only a statistically insignificant collection of data is available for study. Therefore, the characteristic growth curve obtained from the muscular dystrophy group can not be discussed at this time with any great meaning. One of the hopes of this study is that, when completed, it will afford means of evaluating already held concepts of muscle pathology in muscular dystrophy, as well as establishing a method of research orientated to the quantitative assessment of muscle pathology.

The one existing concept which is reexamined is that of an increased variation in dystrophic muscle fibre diameter judged by the microscopic appearance of transverse sections of dystrophic muscle. It is hoped that this study will provide a definite statement on the veracity of the above mentioned observation (see figure 1).

Pearson[7] noted the raised serum levels of lactic dehydrogenase and other enzymes normally located intracellularly, in siblings of Duchenne dystrophy patients who were themselves later to develop dystrophy, and biopsied the muscles of these suspected Duchenne dystrophy cases. These biopsies showed a "typical" pic-

ture of fibre size variation and hypertrophy of individual fibres.

Pearson's observation has a major implication about the pathogenesis of this disease. The connection of raised serum levels of normally intracellular enzymes with disturbed fibre morphology in the yet preclinical stages of dystrophy, may indicate a "leaking" of vital enzymes through a damaged or malfunctioning cell membrane and thus draw attention to this structure as the site of the basic lesion in muscular dystrophy. The inference by Pearson that there may be miscroscopically visible pathology even in utero in children destined to develop muscular dystrophy, would suggest that the muscle biopsy could be used as another screening test for the siblings of muscular dystrophy sufferers. A more useful test would be to distinguish heterozygote female siblings so that potential "carrier mothers" could be detected. However, in our study of dystrophic muscle biopsies, it was found that in any one age group, the specimens varied so greatly in their mean fibre size and standard deviation, so that only the values derived from the pooled fibres or from the average values of any one age group could be seen to fall into any sort of a pattern. This gives little encouragement for the diagnosis of preclinical dystrophy by muscle biopsy, where one is primarilly concerned with the individual case in question, and less with the average tendencies of many cases.

The new approaches opened by this study forecast a greater application of quantitative methods in the study of the histology of this disease. Further work on the slides of these selected cases of muscular dystrophy, will entail an assessment of microscopic pathological features in regard to the age of the patient and to his fibre size and distribution. In this way it is hoped that the differing features of this disease's pathology may be related to each other, to fibre size, and to the patient's age, in a sequential manner, and perhaps in a causal manner.

ACKNOWLEDGEMENTS

The author wishes to express his gratitude to Dr. P. E. Conen, Research Pathologist at the Hospital for Sick Children, for giving him the opportunity of working on this project and for his advice on both the work performed and in the preparation of this paper.

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Abstracts

American Practitioner, Vol. 13, p. 655, (1962). *The* Management of Extensive Lesions of the Male *Genitalia,* K. H. Doolittle et al.

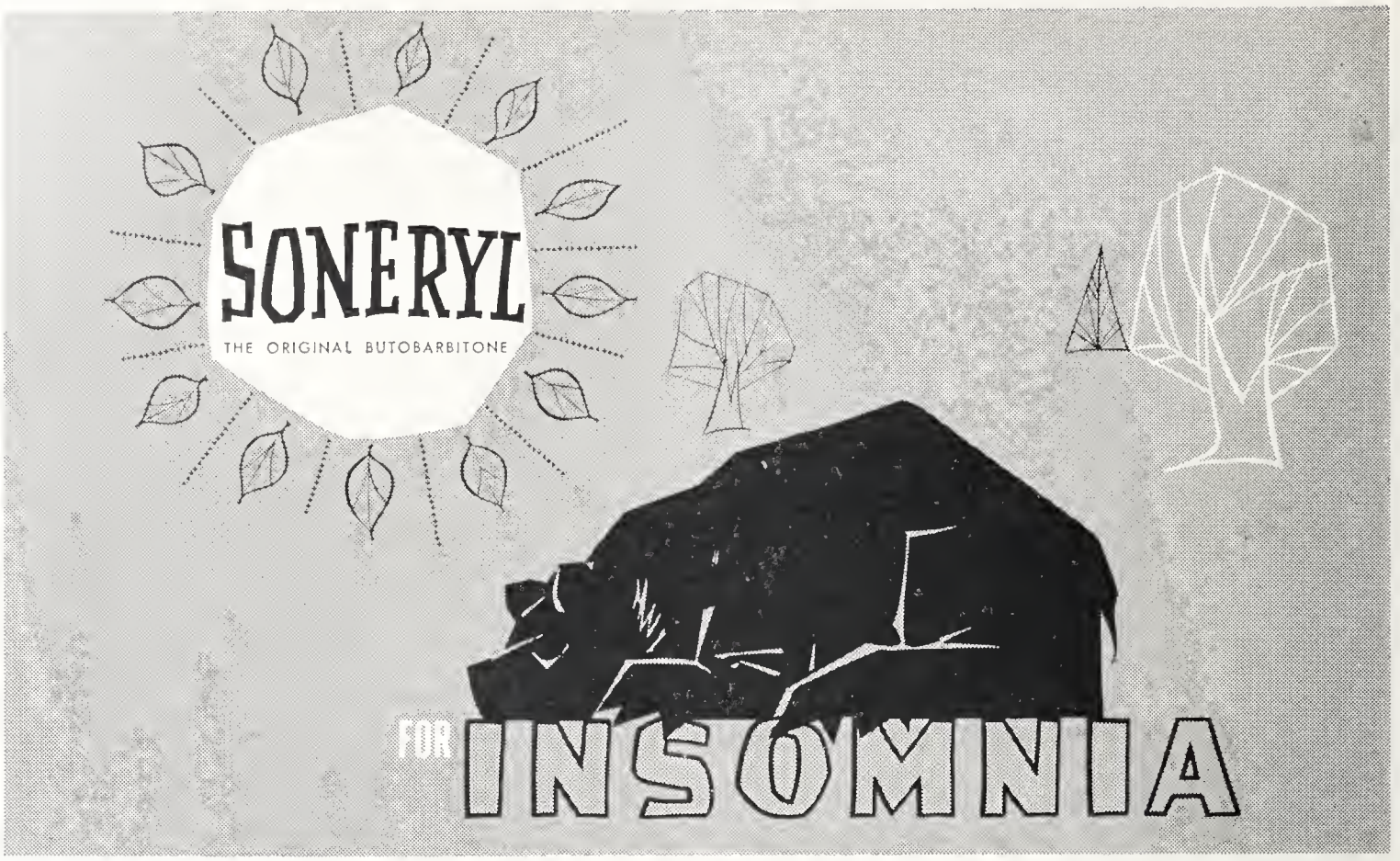
Since extensible lesions of the male genitalia requiring radical surgical procedures are rare, the authors present two cases: one of a young man with condylomata of the penis and one of an older man with basal cell carcinoma of the penis and perineum. The approach to these cases was different in that, with the young man there was a desire to maintain sexual function. In the other case preservation of sexual function was unimportant but a radical operation was imperative to preserve life. The authors feel that the combination of plastic and urologic surgery was more beneficial than if only one specialty had been represented.

Observations on the Value of Mitral Commissurotomy. O. Gialloreto, B. Tardif. JCMA, Vol. 89, p. 589. Sept., 1963.

The authors observe the results of mitral commissurotomy on a series of patients over a period of eight years. Statistics are given regarding the number of deaths, restenoses and satisfactory and unsatisfactory results.

These statistics are broken down to determine relevant factors e.g. results are considered in those cases in which there were incomplete mitral opening, auricular fibrillation, preoperative right ventricular failure, calcification, associated valvular lesions and rheumatic reactivation.

The authors conclude finally that the operation, although palliative only, is a valuable procedure for the relief of secondary symptoms of mitral stenosis.



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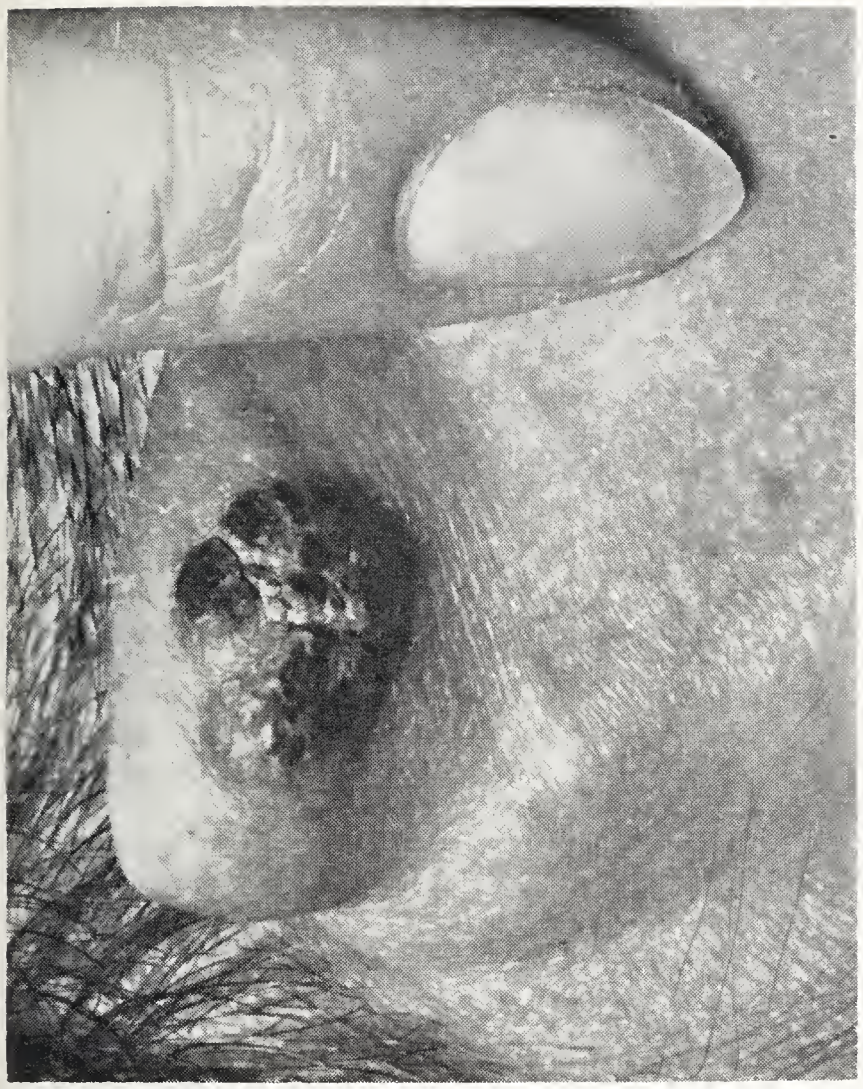

FIGURE 1: Note the characteristic appearance and location of this lesion. What is the diagnosis?

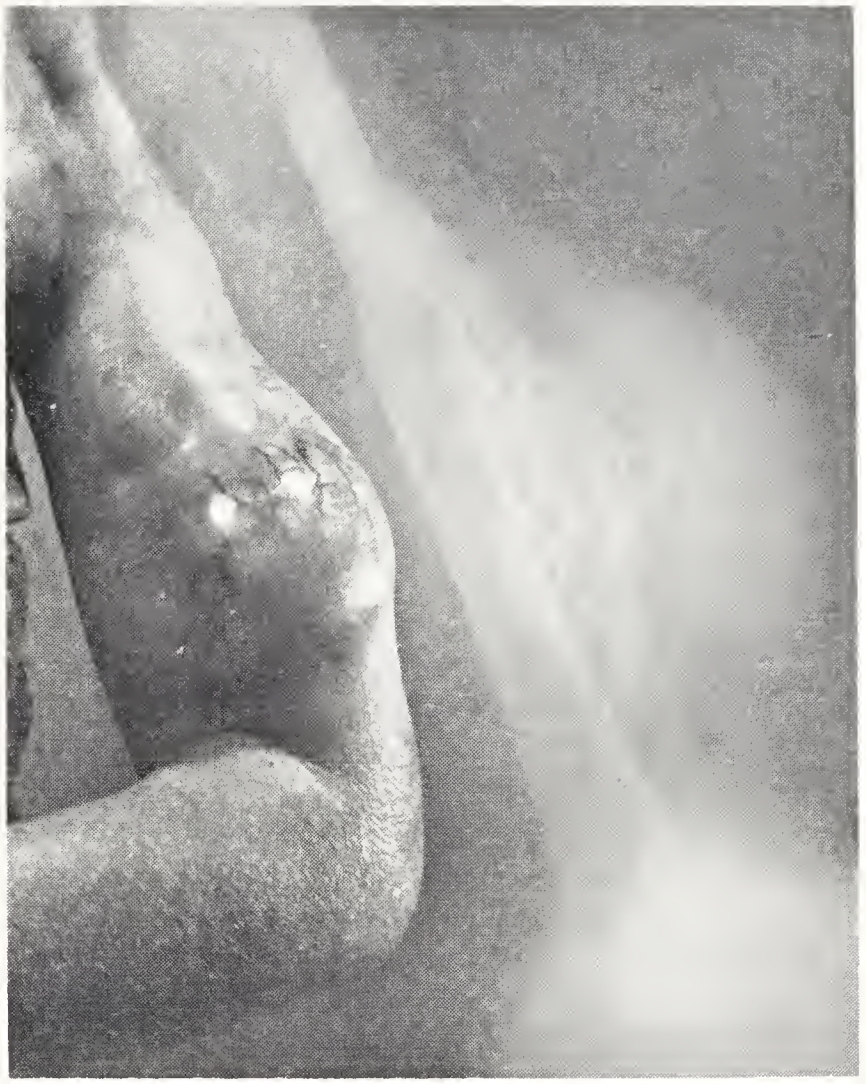

FIGURE 2: Can you recognize this lesion? Main features and treatment?

ON INSPECTION

C. Listgarten 6T4

Photos courtesy *A. Smialowsky*

Answers on page 48

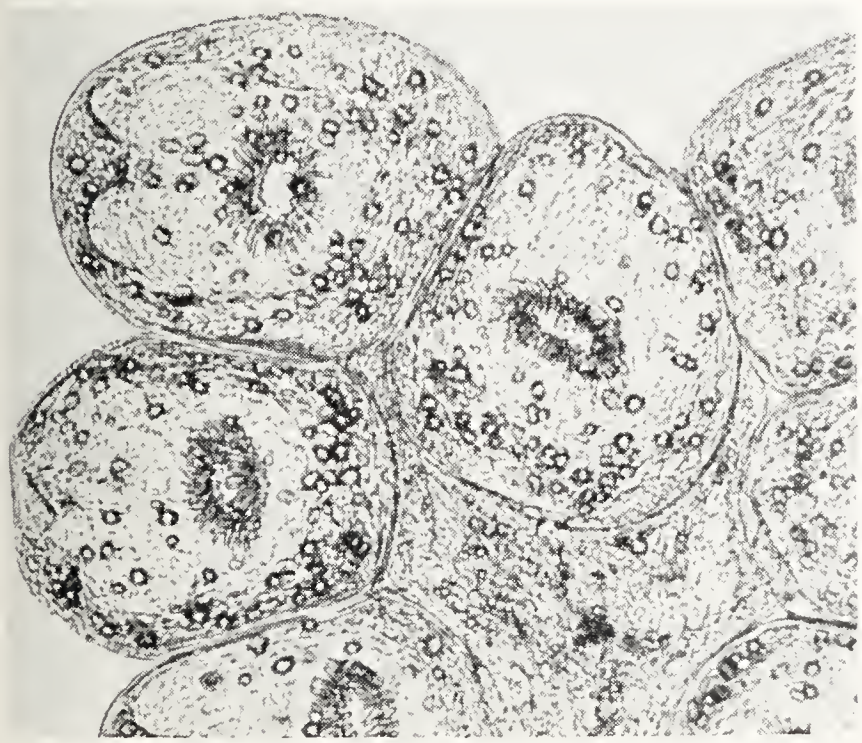

FIGURE 3: This is not modern art. Can you guess?

FIGURE 4: This is a classical picture. Diagnosis? What are the main clinical features?

Recent Advances

THE IMPLANTABLE PACEMAKER

The basic problem with which the science of medicine is frequently confronted in the clinical situation is that of supplementing a function of the human body which has either failed or is inadequate to maintain homeostasis. The methods of doing this are highly variable, ranging from the use of antibiotics as an adjunct to the immune response, to the attachment of an individual to the artificial kidney in renal failure.

The heart is the object of many such aids to its function. Congenital anomalies and defects caused by such diseases as rheumtaic fever are repaired by heart surgery, frequently with an extracorporeal pump-oxygenator taking over heart (and lung) function during the operation. The failing heart is rejuvenated by the use of digitalis. A comparative newcomer in this field is a device to substitute for a faulty conduction system in the heart — the implantable pacemaker.

Due to acquired lesions of the A-V node or bundle, some people suffer from partial, intermittent complete, or complete heart block. These lesions are usually due to arteriosclerotic coronary artery disease causing localized ischemia of the conducting system. This may slow the Ventricular rate to 4-5 beats per minute, cause complete stoppage, or induce ventricular fibrillation. These syncopal Stokes-Adams attacks in the past invariably lead to eventual sudden death. Over the last one and one half years the Cardiovascular Unit of the Toronto General Hospital has been placing internal cardiac pacemakers in certain of these patients to overcome this blocking phenomenon, and has achieved low mortality and morbidity and no complications.

Persons with Stokes-Adams attacks are first tried on a conservative regime of drug therapy — Isuprel Ephedrine, Atropine, Steriods. If they do not respond satisfactorily and have neither a recent infarction nor progressive coronary artery disease, they are considered eligible for operation. Twenty-four hours before operation a temporary pacemaker is inserted under the fluoroscope via an arm vein and wedged into the myocardium; this is used to stimulate the heart, if necessary, prior to and during operation, and is removed within twenty-four hours after operation. At operation an anterolateral thoracotomy is performed, and leads are implanted in the left or right ventricular myocardium one centimeter apart. Positioning seems unimportant. The pericardium is closed with no additional covering of leads. The pacemaker (powered by a mercury battery) is placed, in a Teflon bag to aid in fixation and encapsulation, in a pocket in the axilla deep to either pectoralis major or latissimus dorsi. This gives no discomfort to the patient. An emergency rat tail of the pacemaker is placed well away from the battery unit and subcutaneously, in case of sudden failure of the pacemaker battery. A four week convalescence with appropriate chest and leg exercises to prevent pulmonary complications and throbophlibitis, plus early mobilization, have produced very good results.

Most patients return to active life, including a sixty-five year old female who resumed active nursing duties. No avoidance of electrical appliances seems to be necessary, and the pacemaker gives no interference with aircraft communications so air travel is permissible. The only duty required of the patient is that of taking a daily pulse, since pacemaker fatigue produces an elevated pulse.

Only two deaths have occurred in nineteen patients, who ranged in age from forty-nine to eighty-seven years. Of these two deaths, one was due to aortic valve disease and the other (who was suffering from progressive coronary artery disease) to ventricular fibrillation and acute myocardial infarction.

Interesting is the fact that partial or intermittent complete block creates no problems due to two competing pacemakers (one natural, one artificial), although the patient does have an awareness of arrhythmia.

Electronics has long been utilized in medical diagnosis in instruments such as the ECG and EEG. However, the actual incorporation of an electronic device as a long-term, functional component of the homeostatic mechanism of the body is an important advance and an interesting concept in medical therapy.

ACKNOWLEDGEMENT

I would like to thank Dr. R. O. Heimbecker for the information made available for this article.

Stem-Cells of the Haematopoietic System

M. Blackstein 6T5

Introduction

Many tissues in the adult mammal are in a continuous equilibrium with a balance between production and loss. In a simple "renewal" system such as the skin, various levels of cellular proliferation, maturation, and transformation into keratin, have been described in both functional and morphological terms. The haematopoietic tissue may also be considered to be composed of various levels or compartments. These may be described as

(1) A specialized compartment which consists of fully differentiated cells such as the erythrocyte and granulocyte. These cells are incapable of reproducing themselves and depend on the next compartment for their production.

(2) The second level of the haematopoietic system is composed of cells undergoing maturation. These cells have a limited proliferative ability, and, with increasing division became more mature and enter the first compartment.

(3) The third level is composed of the primitive progenitor cells or the stem-cells which are responsible for the continued production of both themselves and the differentiated cells of the second compartment.

Recent investigations into the nature of the stem cell compartment will be presented in the following discussion.

The Stem Cell Defined:

At the present time there is no agreement as to the morphology of the progenitor cell(s) of marrow, peripheral blood, and lymphatic tissue.[1] Hence any definition of this cell must be made on the basis of the functional capacities[2,3] of the stem cell for:

(1) Extensive proliferation

(2) Self-renewal

(3) Ability to give rise to differentiated descendants

Methods of Study

It would be very satisfactory if normal bone marrow could be removed from an animal and studied in tissue culture where various manipulations could be performed. Attempts to culture marrow have been tried by various workers, but in the "in vitro" situation, one of the above properties is lost; that is, either the culture comes to be made up of progressively more differentiated cells with the result that the culture dies out, or some transformation occurs and only proliferation without differentiation arises.

However there are two methods of in vivo study. The first of these methods is the spleen clonization technique of McCulloch and Till, utilizing recovery processes in haematopoietic tissue of mice given sublethal or lethal irradiation. This method[4] consists of the intravenous injection of an appropriate number of cells from isologous donor mice into recipients which have been previously given sufficient radiation (800-1000 rads) to suppress their own haematopoietic system. The source of these cells are from sites of haematopoiesis, bone marrow, spleen and foetal liver. The recipient mice are then sacrificed at nine or ten days after injection and their spleens are removed. Gross examination reveals round discrete nodules embedded in the spleen, which can be easily counted. Microscopic examination of these nodules reveals that they consist of large numbers of haematopoietic cells, many of which are dividing, and often within a single colony, differentiation along three cell lines; erythrocytic, granulocytic, and megakaryocytic, can be seen.[5]

The ultimate value of the spleen colony technique however is based on the fact that these colonies are clonal in origin. (a clone is a population of cells derived from a single parent cell). The clonal origin of the colony is most important since if the colony arose from a mixed population of cells, a response by a minority of the cells could result in false conclusions about the behavior of the majority of the cells. In addition, the only method of establishing that a cell can proliferate extensively, is to allow it to form a clone.[6]

The evidence that these colonies are indeed clones come from several sources. The first two points are indirect.

(1) The graph[4] relating the number of spleen colonies to nucleated cells injected intravenously is approximately linear and passes through the origin on extrapolation.

(2) The radiation survival curves[4,8] of cells which form colonies closely resemble the survival curves ob-

tained for single mammalian cells[7] in culture or tumor transplant.

(3) Direct evidence[5] however was furnished by cytological examination of spleen colonies prepared from marrow irradiated "in vivo". This was done in the attempt to induce abnormal karyotypes, for if a colony forming cell was hit by sufficient radiation to induce a gross chromosomal change without imparing the ability of the cell to proliferate, it would be expected that all the descendants of this cell would carry the same marker. Unique abnormal karyotypes were indeed seen in four colonies out of a total of 42, and the cells of each colony all carried the same marker characteristic for that colony. Since it is highly improbable that the same chromosomal abnormality could be induced in two or more cells, simultaneously, by such a random event as radiation, one can conclude that only one cell is responsible for the production of the spleen colony and hence the colonies are clones.

The only other functional test which colony forming cells must pass is the ability for self-renewal. This property was shown[3] by disecting out individual spleen colonies. Suspensions were made and these were injected into a second group of radiated recipients. (It should here be mentioned that not all colony forming cells go to the spleen, the majority of them in fact return to repopulate the marrow spaces. However, a constant fraction of these cells do go to the spleen and from this fact the total number of colony forming cells injected can be estimated). When these recipient animals were sacrificed, it was observed that the number of colony forming cells arising from an individual colony followed a heterogeneous distribution, most colonies giving rise to about 10 colony forming cells by the 14th day, while a few colonies contained over 200 such cells. No characteristic of the colony such as size or color could be correlated with the number of colony forming cells that could be recovered from a single colony and further research is being done along these lines.

The above experiment has shown that the colony forming cells possess the following properties.

(1) Capacity for self-renewal

(2) Pluripotential ability (colonies have been shown to contain erythrocytic, granulocytic, and megakaryocytic precursors).

(3) Capacity for extensive proliferation (a colony contains 16 cells by the ninth day of development.)

These are the properties that were earlier listed as being the basis of the stem-cell compartment. Therefore we may conclude that the spleen colony technique is a method of "in Vivo" culturing of a single stem-cell of the mouse haematopoietic system. Response of the Colony Former to Differentiation Pressures.

Differentiation Pressures

The effect of erythropoietic stimulation forms the basis of a second assay system for stem cells, devised by Gurney, et al.[9,10,11] These authors have presented evidence to indicate that erythropoietine acts directly on the stem-cell compartment to induce the transformation of stem-cells to erythroblasts. If this were indeed the site of erythropoietine action, one would expect to see a decline in the number of colony forming cells which could be recovered from spleen or bone marrow coincident with changes reflecting an increased red blood cell production (such as an increase in Fe^{59} uptake by the spleen and an increased reticulocyte level in the peripheral blood).

In the experiments designed to test this hypothesis,[12] mice were placed in an hypoxic atmosphere in order to increase the levels of endogenous erythropoietine. After three days a maximum rise in the Fe^{59} incorporation by the spleen was seen, at four days the reticulocytes of the peripheral blood reached their maximum level. However, only a gradual decline in the number of colony forming cells recovered from the spleen occurred, so that by the 15th day of hypoxia, the number of colony forming cells recoverable from the spleen had fallen to 10% of the original level.

But throughout the entire period of hypoxia, no decline in the number of colony forming cells recovered from bone marrow was noted. These experiments suggest several possible explanations with respect to differentiation pressures:

(1) The erythropoietine sensitive cell does not appear to be equivilent to the colony forming cell since the minimum values for spleen colony forming cells was observed after 10 to 15 days of hypoxia, several days past the peak of reticulocytes and iron incorporating cells.

(2) Colony forming cells are themselves not sensitive to erythropoietine, but erythropoietine sensitive cells are included among the progeny of colony forming cells. This may indicate that the decline in colony forming cells in the spleen of hypoxic erythropoietine is a humoral substance probably produced in the kidneys in response to hypoxia. It can be obtained by various extraction procedures from sheep made anaemic by bleeding, or by phenylhydrazine; or from the urine of severely anaemic human subjects.

mice may be a consequence of a depletion of the pool of erythropoietine sensitive cells with the colony forming cell differentiating to restore this pool.

(3) The failure of a decline in the colony forming cells of the marrow suggests that cells in certain locations may be less responsive, or receive smaller stimulation, than cells in other sites and would constitute a reservoir from which the pool of colony forming cells could be regenerated when the stress was removed.

A second series of experiments are now underway to test the effect of another agent which may act to induce the differentiation of stem-cells. This drug known as Lipopolysacchoride (Difco) is the O antigen of Salmonella Typhosa. It has been previously shown[13] that this agent has the ability to mobilize granulocytes into the peripheral blood from the marrow. It has also been shown[14,15] that this drug acts as a radiation protector in mice increasing the L.D. 50/30 days and promoting increased haematopoietic recovery from irradiation. Preliminary experiments indicate that injection of this drug previous to radiation results in an actual *increase* in the number of stem-cells and that this effect takes about 24 hours to reach a maximum, perhaps indicating at least one cell division in the stem-cell compartment. A future series of experiments using multiple injections of the drug and injections of the drug combined with hypoxia will soon be undertaken and it is hoped that these results may shed light on the phenomenon of depletion of the stem-cell compartment.

The experiments and problems illustrated above may seem somewhat remote from the field of clinical medicine and the relationship of the stem-cell to disease. However, it is considered by many investigators that the problem of stem-cell regulations are of a primary nature in the pathogenesis of clinical entities such as the anaemias and leukaemias. It is hoped that studies on the functional behavior of the stem-cell compartment will increase our knowledge about the changes which occur in the above disorders and increase our understanding of both normal and pathological conditions involving cellular proliferation and growth.

ACKNOWLEDGEMENTS

I would like to thank Drs. E. A. McCulloch and J. E. Till for the opportunity afforded me this summer to work in the laboratories of the Department of Medical Biophysics, where much of the work cited in this article was carried out.

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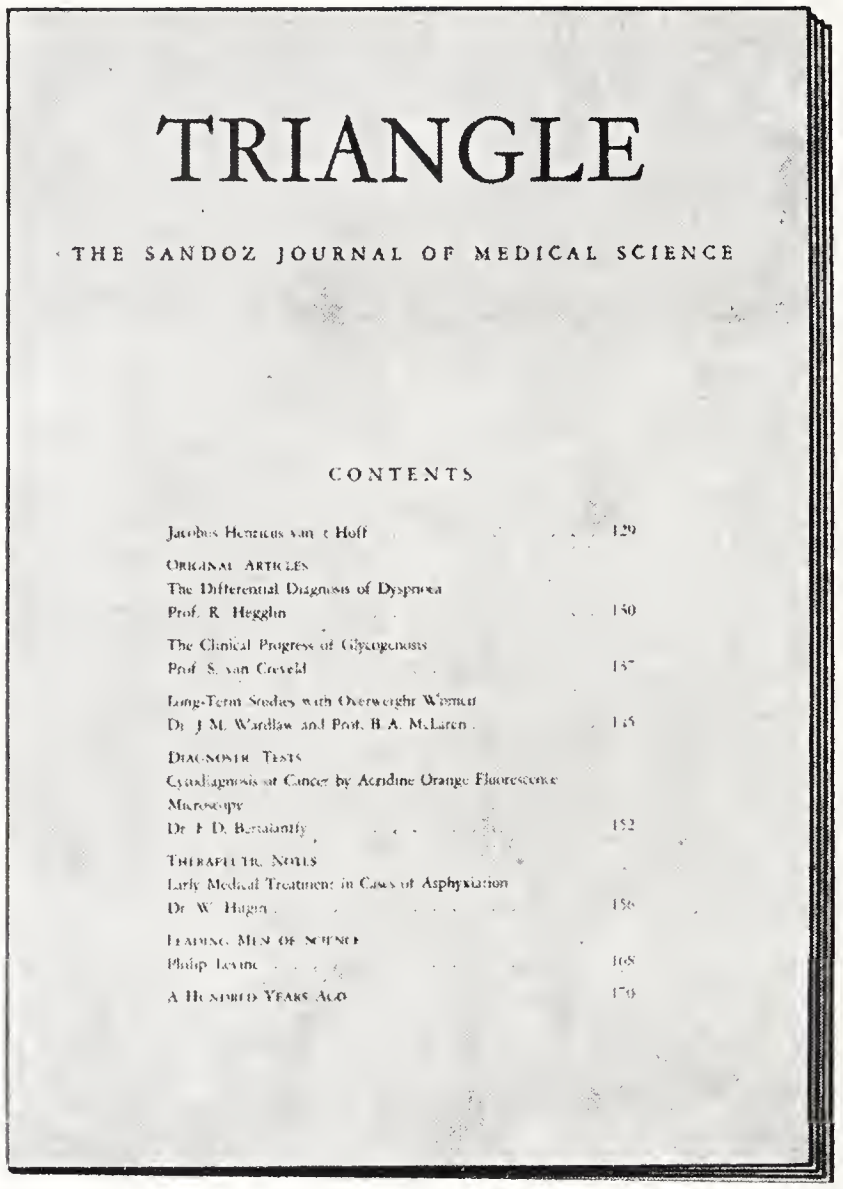
Abstract

JCMA, Vol. 89, p. 705, (1963). Baird, R. J., et al. *Protection of Renal Function During Surgery of the Abdominal Aorta*

Acute renal failure is occasionally a result of operations in which the abdominal aorta is temporarily occluded below the renal arteries. This article studies a series of such operations and suggests a possible means or preventing renal failure. In a series of 55 patients, 28 received blood only while 27 received either mannitol or 5% dextrose in water intravenously. Mannitol is an inert, non-toxic diuretic filtered at the glomerulus and not reabsorbed by the tubules. This was given preoperatively and operatively and caused a diuresis operatively and postoperatively thereby preventing anuria and renal failure.

It is suggested that renal failure occurs as a result of the following mechanism: renal ischemia leads to decreased glomerular filtration and tubular hypoxia. The decreased volume of filtrate is completely reabsorbed in the tubules which tend to collapse. Later the hypoxic cells swell and occlude the lumens causing anuria. By causing a diuresis the lumens are kept patent and anuria prevented. It is suggested that this may aid in the prevention of renal failure.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SANDOZ PHARMACEUTICALS SANDOZ DORVAL, P.Q.

Effect of Anti-Parkinson Drugs on Thermoregulation

Fred Simon 6T5

Introduction

Homeothermic animals maintain a constant body temperature in spite of wide variations in environmental temperature by maintaining a balance between heat production and heat loss. The heat is constantly being produced by the metabolic activities of the body which, under resting conditions, amounts to 37-40 kcal. per square metre per hour. The heat thus generated by the metabolic activities of the organs is relatively constant but the contribution of the skeletal muscle is variable and reaches a maximum in cold climates by the process of shivering.

Heat is conducted from the interior of the body to the surface by the blood stream where it can be dissipated by radiation, conduction and convection to the cooler environment. The temperature of the skin is determined by its blood flow and hence an increase in blood flow through the skin due to cutaneous vasodilatation will cause an increase in heat loss. Accumulating evidence indicates that this vasodilatation is caused by the activity of the sweat glands and mediated through bradykinin.[1]

Heat is continuously being lost from the body by the evaporation of water from the lungs and skin even under resting conditions. The air entering the lungs is continuously being saturated with water vapour while insensible perspiration is uniform over the entire body surface at a fairly uniform rate which is largely independent of environmental conditions. In extremely warm environments thermal sweating is the body's main defence mechanism to increase heat loss. The sweat must evaporate from the body's surface to produce the desired heat loss which can reach a maximum of 1000 kcal. due to the evaporation of 12 litres over a period of 24 hours. If there were no heat loss the body temperature would rise 1°C. per hour even under basal conditions.[2]

The central control of thermoregulation appears to rest in the hypothalamus.[3] Structures in the anterior part of the hypothalamus appear sensitive to a rise in temperature and local heating of these structures will result in sweating and vasodilatation. Similar structures in the posterior part of the hypothalamus are sensitive to a fall in temperature and local cooling will result in shivering and vasoconstriction. However there is still debate as to whether the main thermal control of cutaneous blood flow is exerted from skin temperature receptors or from the centres in the hypothalamus.[4]

Drugs can influence thermoregulation either by a direct effect on the centre or by a peripheral action which can alter shivering or sweating; vasoconstriction or vasodilatation. The antipyretic effect of the salicylates appears due to its stimulating action on the heat-dissipating centre. Reserpine is a drug which exhibits both a central and a peripheral action. It has been found to liberate catecholamines and 5-hydroxytryptamine from their various stores in the body both peripherally and in the brain stem. This peripheral depletion of norepinephrine from the vasomotor nerve endings would prevent vasoconstriction and hence increase heat loss. Accordingly, the toxicity of reserpine is very much greater at cold temperatures than in a warm environment.[5,6] Sympathomimetic agents such as ephedrine and amphetamine produce pyretic effects which are partly due to peripheral vasoconstriction and hence a decrease in heat loss[7] whereas histamine has been shown to decrease the body temperature of rats probably as a result of an added heat loss due to vasodilatation.[8]

During the past summer I have studied the effect of several anti-Parkinson drugs; mescaline, a psychotomimetic drug; and methocarbamol, and inter-neuronal depressant which is used as a muscle relaxant;[9] on the thermoregulation of rats. Since both Parkinson tremor and shivering are involuntary, rhythmic muscular contractions it was decided to determine whether drugs which are used to control Parkinson tremor would affect the shivering induced by a cold environment.

Adult female rats were arranged in groups of six and each group of animals was injected intraperitoneally with a different drug. The animals were then placed in environments at either 4°C, 25°C, or 32°C and half-hourly rectal temperatures were recorded using a thermocouple. The metabolic rates of the injected animals at these three temperatures were also determined and electromyograms were taken using a Grass polygraph connected to the animals shivering in the cold-box at a temperature of 0°C.

The results indicate that the anti-Parkinson drugs exert no effect on shivering and that the animals can survive quite satisfactorily when injected with these drugs at all three of the temperatures employed in this

experiment. These results agree well with those of Stuart et al. who showed that atropine had no effect on the shivering of cats placed in an environment of 5°C.[10] The inability of atropine and the anti-Parkinson drugs, which are classed as cholinergic blocking agents, to exert an effect on body temperature does not agree with the work of Burns and Dutta which states that "the maintenance of body temperature depends upon a mechanism in which acetyl choline plays a part."[11]

Methocarbamol at a dose of 320 mg./kg. was found to produce a complete muscle relaxation and a severe hypothermia at 4°C which proved fatal to non-acclimated animals but was not fatal to cold = acclimated* animals. (See figure 1) The ability of the cold = acclimated animals to survive in the cold without shivering depends upon an increase in heat production which is sufficient to balance the increase in heat loss due to the complete muscle relaxation. This "non-shivering thermogenesis" enables the cold-acclimated animal to live out his normal life span in a cold environment.[12] An indication of the extent of this extra thermogenesis is the fact that the metabolic rate of cold-acclimated animals is 20-30% higher than that of non-acclimated animals when both are measured at a temperature of 30°C. It is only slightly higher when the measurement is made at 2°C. but shivering does not occur in the acclimatized animals. The bulk of this extra metabolism is thought to occur in the muscles but other organs such as the kidney and the heart are also thought to participate. To what extent this non-shivering thermogenesis occurs in man is not yet fully understood.

SUMMARY

Anti-Parkinson drugs are shown to have little effect on shivering and on temperature regulation in general. Cold-acclimated rats possess a 'non-shivering thermogenesis' which enables them to survive a dose of methocarbomol (a skeletal muscle relaxant) which produces a fatal hypothermia in non-acclimated animals.

ACKNOWLEDGEMENTS

I wish to thank Prof. E. A. Sellers, Department of Pharmacology, for the guidance and encouragement during the course of these investigations.

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° Animals which have lived at a temperature of 4°C. for more than 5 weeks.

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Some Recent Research In Experimental Cardiovascular Surgery

Ronald M. Zahoruk 6T5

Within the past decade the medical student has become increasingly aware of the work of the cardiovascular surgeon. No doubt, the reason for this interest lies in the fact that cardiovascular surgery has made a small but dramatic "dent" in the total sum of pain, invalidism and death caused by a wide variety of congenital, acquired and degenerative lesions of the cardiovascular system. It is hoped that this report on some recent experimental projects, carried out under Dr. Raymond O. Heimbecker of the Toronto General Hospital Cardiovascular Surgery Department, will meet with at least a small part of this wide student interest. These reports, while only a segment of recent work in one laboratory, will serve well to illustrate the wide variety of perplexing problems which hundreds of similar experimental cardiovascular research laboratories throughout Canada and the United States are attempting to overcome.

I. *High Porosity Two-Stage Arterial Graft*

A large portion of our older patients suffer from various degrees of chronic occlusive or aneurysmal arterial atherosclerosis. A much smaller but younger group of predominantly male patients suffer from peripheral ischaemia due to thromboangiitis obliterans. It is sometimes possible to replace segments of the larger vessels so affected with recently developed "solid-walled" prosthetic vessels made with various new plastic materials. Often the patient is relieved of symptoms and disability. However, the five year patency-rate of such prosthetic segments even in larger vessels such as the abdominal aorta, is not as good as would be desirable. Occlusion of the artificial vessel is thought to be related to the inadequate vascularization of the endothelium and connective tissue which develops soon after the prosthetic segment begins to carry blood. With progressive fibrosis on top of the old necrotic tissue lining the artificial vessel, there is ultimate occlusion. This has lead to investigation of prosthetic vessels made with materials having a large number of pores. Briefly, the main theoretical advantage of thees pores is that they should allow "vasa vasorum" to grow into the tissue lining of the vessel in order to nourish it and hence prevent eventual occlusion due to necrosis, calcification and fibrosis.[4] But the difficulty with very highly porous prosthetic vessels is that they do not prevent haemorrhage in the immediate post-operative period, although many attempts have been made to seal the pores temporarily with resorbable materials. About two years ago, Dr. Heimbecker and associates began to implant artificial vessels made of highly porous Teflon, subcutaneously in dogs.[10] Four to five weeks later, after the pores were blocked off by the fibrous encapsulation of the natural foreign body reaction, these prosthetic-autograft "scar tubes" were used to replace segments of the abdominal aorta. in either the same dog or in an acceptor animal. Hence the fate of homograft and autograft two-stage prosthetic grafts was made. We

FIGURE 1: High Porosity two-stage arterital prosthesis in the dog aorta after seven months implantation. Note the smooth glistening inner surface with no fibringus preeipitate or ealcification evident. The teflon mesh seen through the intima was previously implanted subeutaneously in the same animal to allow for fibrous tissue eneapsulation and closing of the pores in the mesh.

sacrificed such dogs at various time intervals post-operatively to evaluate the state of the graft. Although this investigation is continuing, the results so far are encouraging. There is a high rate of 100% patency (85%) even after periods of implantation of up to one year. Microscopically the amount of calcification and necrosis in the fibrous tissue lining the vessel is

less than one expects to see in "solid-walled" artificial vessels presently used in clinical practice (Figure 1) Clinical trials in human patients using both the two-stage homograft and autograft principle are being planned.

II. *Disposable Pump Oxygenator*

In the cardiac patient requiring an open-heart operation, an extra-corporeal pump is used to "replace" the work of the heart during the surgical procedure. In addition, oxygenation of the blood must be performed by an "artificial" mechanical lung. The most widely used oxygenators are the bubble and the disc oxygenators. While these have proved successful in minimizing trauma to the cellular elements of the blood and oxygenation of haemoglobin, the process of cleaning and subsequent sterilization for the next operation is a tedious task. Hence a great deal of recent research has been aimed at developing a disposable, high surface oxygenator made of materials which allow complete oxygenation with minimal red cell haemolysis. Yet the oxygenator must be cheap enough to be disposed of after each open-heart procedure. If long term support of the failing heart by means of external pump oxygenators becomes a clinical reality, the disposable oxygenator will probably play an important part in such therapy. Our early trials with an oxygenator made of a number of vertical, high-surface, highly porous, industrial fiberglass mats through which venous blood seeps before entering the pump, have been made. Haemoglobin oxygenation with even as few as twenty such 15" x 24" fibreglass mats has been complete in every trial. This is an amazing accomplishment in view of the fact that in the early years, when open-heart surgery was still a dream, some physiologists doubted that a mechanical apparatus which could imitate the 75 square metres of diffusion membrane in the human lung, would ever fit into the operation room.[11] While haemolysis of the rather tender dog red cells has been somewhat high with this simple industrial material, it is hoped that by some sort of special pretreatment of the fibreglass, trauma to red cells will be decreased. In this connection it should be pointed out that, in the dog, pump survival results are difficult to evaluate for even the healthy dog is a notoriously poor candidate for extracorporeal circulation. Most experienced experimenters in the field would agree that even under the best circumstances, a 30-40% death rate after pump runs in dogs, can be expected. Fortunately, seriously ill human beings tolerate extra-corporeal circulation much more satisfactorily.

III *Follow-Up of Homograft Aortic-Valve Transplant*

The prize of the Banting Institute Animal Laboratory for the past two years has been a black Labrador retriever. This animal was the longest survival of a total of seven survivals in which the laboratory surgical staff had replaced the tricuspid valve with a specially prepared donor aortic valve. Three years later this dog—the world's longest such survival—was still murmur-free! A right heart catheterization which we carried out this past summer revealed only a minor degree of insufficiency. Such a result is certainly gratifying. Theoretically, the normal human homograft valve should be less likely to undergo host rejection, for the human valve, like the graftable human cornea, is almost avascular. Accordingly, a successful replacement of a diseased mitral valve in a human patient was accomplished for the first time by Dr. Heimbecker in the spring of 1962.[2] Unfortunately the patient died a month postoperatively of a chest infection; there were no murmurs and the valve-cusps appeared normal and in good position at autopsy.

IV *Haemodynamic Studies With Angiotensin Aldosterone and L-Epinephrine**

One small project in the laboratory, under my supervision, involved a study of the haemodynamic effects of angiotensin, epinephrine and aldosterone, singly and in combination. The renal hormone, angiotensin is an intense peripheral vasoconstrictor which acts on the adrenal cortex to release aldosterone which is known to act on the kidney to reabsorb sodium. Extensive experiments carried out by Hatcher and Binnion in the Queen's University Department of Physiology, have shown that while l-epinephrine increases cardiac output and angiotensin acts to raise blood pressure, these two drugs in specific doses increase output and blood pressure to a higher degree than each drug achieves individually dose for dose.[1] We were interested in observing the effect of adding aldosterone to this mixture since aldosterone has been shown, both clinically and experimentally, to potentiate and lengthen the effect of pressors that act on the heart and vessels.[7] The chest of experimental dogs was opened and the probe of the electromagnet square-wave flow metre was placed on the root of the aorta to continuously measure slight instantaneous output changes induced by these drugs. While our series is far too small to be conclusive, it appears that aldosterone does lengthen slightly the time during which cardiac output and pressure increase with mixtures of angiotensin and l-epinephrine. If such increased efficiency of the heart could be greatly prolonged, it is not hard to imagine clinical applications for such drug combinations.

V. *Some Thoughts About Future Research*

Twenty years from now the cardiovascular surgeon

will present operative armentarium may probably be more a "vascular" than a "cardiac" surgeon. This will come about largely because the incidence of rheumatic fever — the principal cause of most operable acquired valvular heart disease—has very fortunately decreased to a level which is about one fifth of that which existed prior to the antibiotic tera. Still the search for the ideal prosthetic or homograft valve must continue, for ultimately a complete valve replacement is the only answer in a large group of patients with severely diseased valves[3,5] The cardiovascular surgeon of the future must also strive to develop new and better prosthetic vessels to replace the occluded blood vessels much smaller than the 5mm. limit beyond which he presently cannot pass. And he had better start thinking about it now, for his own coronary arteries are well started on the road to occlusion even before he finishes medical school. Certainly, coronary artery disease, the most common heart disease for which the cardiovascular surgeon can do frustratingly little, must always remain a challenge to all of medicine. In an imaginative American centre workers are actively developing a two chambered mechanical heart with which the surgeon might totally replace a severely diseased heart. A well known Canadian surgeon, Arthur Vineberg, has devoted a lifetime to revascularization of the ischaemic heart.[9] The problem remains and is large enough to merit at least a few more such long term attempts.

*I wish to thank Dr. R. O. Heimbecker, Dr. R. W. Gunton and Dr. E. D. Wigle for guidance; and Miss Freda Felgar, Mr. Frank Benoit and Mr. Kenneth Burley for patience and advice in completing my project.

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Abstracts

Annals of Internal Medicine, Vol. 59, p. 165, (1963) *The Seasonal Incidence of Complications of Peptic Ulcer,* S. Z. Ahmed et al.

While it is generally believed and taught that peptic ulcers have seasonal exacerbations, this has never been definitely proved because of difficulties in subjective evaluation of symptoms. In the series of cases studied by the authors, the criteria for exacerbation used was the incidence of hemorrhage or perforation, the onset of which is unmistakable to the patient.

The authors reviewed 495 case histories with a diagnosis of perforation or perforation. A review of the literature revealed that while some authors favored the seasonal variation theory and others did not, adequate proof for both stands was lacking.

Using statistical analyses the authors came to the conclusions that, in their series at least, the incidence of hemorrhage and perforation did not vary significantly with season; the values for exacerbation which they noted are: winter 24.6%, spring 24.8%, summer 21.6%, autumn 29.0%.

JMCA Vol. 89, p. 766, (1963) J. D. Hermann, *Medicine in Malaysia*

This article by a member of the staff of the University of Singapore (at present the only Malaysian medical school) descirbes various aspects of medicine in this new nation.

The standard of medical education is high and facilities are improving. About 100 students are graduated in Singapore and about an equal number are overseas especially in Commonwealth Countries. Of interest is the fact that only a few Canadian medical degrees are recognized out of the total number of North American universities. No specialty colleges are present in Malaysia.

Medical practice is both private and state-controlled and generally of a high standard. The author discusses some of the unusual clinical problems met and some of the complications caused by a multiracial population of varied religions and languages. Finally, he expresses the opinion that Malaysia is gradually and successfully advancing to a state of modern health and medicine.

Recent Advances

CLINICAL SPATIAL VECTORCARDIOGRAPHY

The electrocardiogram (ECG) has become a standard clinical procedure in medical practice with an important role to play in the diagnosis of cardiac disease. However, the ECG gives only a limited picture of the electrical activity of the heart. The vectorcardiogram (VGG) has been found to detect the changes in this cardiac electrical activity that the ECG does not reveal.

The basic principles underlying vectorcardiography are identical to those of electrocardiography-muscular contraction and relaxation produces electrical changes which can be detected by electrodes placed on the body surface. A vector is a mathematical symbol used to represent a force; it takes the form of an arrow which points in the direction of the force, and whose length represents the force magnitude. At any one instant the total electrical forces in the heart may be represented by a single resultant vector. This resultant vector changes from instant to instant throughout the cardiac cycle, so that a line drawn through the tips of the resultant vectors gives a summary of the electrical activity of the heart over its entire cycle. The difference between the ECG and the VCG lies in the degree to which this electrical activity is summarized. Any of the standard leads of the ECG give a resultant recording in one plane only; the VCG gives a reading which utilizes two planes. This is done by resolving cardiac activity into three planes by a special system of leads—the X component acting transversely in a horizontal direction, the Y component acting vertically, and the Z component in an anteroposterior direction. Combination of any 2 of these 3 components gives a resultant recording in 2 planes.

The VCG utilizes the cathode ray oscilloscope to record its results. The X components on the horizontal plates and the Y component on the vertical plates produces a frontal plane projection of heart activity. Similarly, the sagittal plane projection utilizes the Y and Z components, and the horizontal plane projection the X and Z components. The tracing obtained for each projection is called the vector loop. It consists of three portions—the QRS loop of ventricular depolarization, the T loop of ventricular repolarization, and the P loop of atrial depolarization.

Dr. H. Abramson of New Mount Sinai Hospital is doing the only routine clinical work with the VCG in Toronto. He is also doing, and has done, investigation into the scope and potentialities of the VCG. Some of this is quoted here. The VCG has been found to detect myocardial infarctions which are missed, or in which the diagnosis is dubious, with the ECG. This has been proved statistically for the interior and anterior wall and diaphragmatic infarctions. These detected changes are in the QRS loop, a stable component of the vector loop in which changes are very significant. This increased accuracy is graphically illustrated by the following case history.

> Mr. X was a young man of 37 years, with a history of severe, non-specific chest pain. There was a family history of coronary artery disease. All ECG recordings were normal except for one which showed — evidence of posterior wall infarct. This vanished on the following day. A VCG showed definite evidence of posterior wall infarction.

Such a definitive diagnosis is of great aid in the adequate treatment of such patients.

The VCG has also proved of use in the differentiation of ostium primum and ostium secundum atrial septal defects. Although differences are also shown with the ECG, they are more consistently demonstrated by the VCG. This is of decided value in pre-operative assessment of patients with atrial septeal defect, since the more centrally placed secundum defect may be cured by open heart surgery using only hypothermia, while the primum defect usually involves the A-V valves and requires the use of the heart-lung machine.

The value of vectorcardiography as a diagnostic aid is still being assessed. It would appear, however, that it has a definite role to play in routine clinical medicine.

B. E. Koehler.

Abstract

The Pathology of Liver Cirrhosis in Patients with Cystic Fibrosis of the Pancreas: K. J. Shier, R. C. Horn, Jr. J.C.M.A. Vol. 89, No. 13, p. 645 (1963).

Cirrhosis of the liver occurs in nearly 25% of cases of cystic fibrosis of the pancreas. It arises by concretions of inspissated mucoid secretions of the bile duct epithelium causing focal inflammatory reactions with extension into and fibrosis of the liver. A further factor of metabolic disturbance of hepatic function due to pancreatic insufficiency has also been suggested.

Two detailed case histories illustrating typical morphological changes are presented by the authors and a discussion is presented in an attempt to explain the development of some of the gross and microscopic features of the disease.

Sulfonamides — Levels in Blood, Urine and Saliva

In the wonderland of miracle drugs, an old, standby is at the moment being rediscovered. The sulfonamides are finding increasing popularity in therapeutic trials. The major reason, of course, is the high incidence of toxicity with newer drugs, and the realization that a conservative plan of therapy reserves more potent agents for more serious disorders.

In this light, our summer work consisted of the study of sulfamethylthiadiazole, one of the many sulfonamides developed in the late 1930's. This particular agent has been used in urinary infections for a number of reasons. It is said to possess limited toxicity, to be highly soluble at usual urinary pH levels, and to be very slightly acetylated. These properties are of obvious benefit for urological disease. When coupled with the rapid excretion and high urinary levels found in many trials, its usefulness is easily seen.

For the current study, sulfamethizole (the generic name), was supplied in tablets of varying sustained release times. Therapeutically, this should allow a more sustained urinary level. Our purpose, however, was to determine the distribution, absorption and excretion of the drug. These properties are commonly required in the pharmacologic evaluation of any drug, and necessitate the development of biological assays for drug content.

By the traditional review of the literature and by the work carried out during the summer, a method of analysis suitable for our experiment was devised. Its major principles were developed by Bratton and Marshall [1] in 1939, and refined by Frisk [2] in 1942. It consists of the diazotization of the free primary amine in the para-position, found in almost all sulfonamides. The diazo compound is then coupled with an aromatic amine, to give an azo dye whose intensity is measurable in a colorimeter.

Using this method, a series of standard curves was constructed. From these, drug concentrations in blood, in urine or any biological fluid can be determined. This seemingly minor effort, then, was the basis for beginning experimental work.

Any sulfonamide in the body is absorbed to some degree in the bloodstream. A large percentage is then protein bound; while a varying amount is acetylated. the drug exists in the bloodstream, then, in free and acetylated forms, and is excreted in the urine in similar composition. For our purpose samples of blood, of urine, and of saliva were required, and measurement of both free and acetylated sulfonamide was carried out.

The drug, in four varying timed-release tablets, was given in double-blind fashion to 8 subjects. Two further subjects acted as controls, taking sulfadiazine, a popular sulfonamide in common use. Blood, urine and saliva samples were taken from each subject at times O, ½, 1½, 3, 6, 12, 24, and 48 hours. To complete the experiment all drugs will be given to all subjects so that a total of five experimental runs will be carried out.

In the first run, the only one completed during the summer, the following sample results were obtained. Preparation A was noted in urine and blood after one-half hour. Blood levels reached 3.1 mg. % in free form, 3.9 mg. % as total drug. The difference is assumed either acetylated or conjugated with glucuronic acid [3]. Urine levels ranged to 4.5 mg/ml after a one gram dose. Recovery ran from to 70 to 100%.

With the other preparations, blood levels are seen to be almost uniformly lower, while recovery ranges from 40 to 75%. Acetylation is noted as averaging 4 to 10% of recovered drug.

In a study such as this, a great problem is noted with individual variations in human subjects. Some will not acetylate the drug appreciably, while others may acetylate 10% of the excreted material. In order to obviate the problem, as noted above, more trials are required, until the effect of each drug in each subject can be compared. This forms the basis for continuing the work during the year, and collecting data until reproducible results are obtained.

At the moment, with only one-fifth of experimental work completed, some conclusions can tentatively be reached. The drug is noted to be only slightly acetylated. It is rapidly excreted, and reaches therapeutic levels in the urine without high serum levels. The individual variability of absorption and acetylation while making the study incomplete, makes it more interesting to the medical-student-cum-researcher, and opens the way for continued drug investigation.

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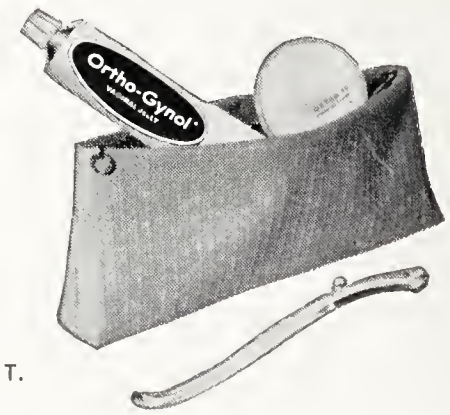

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"It was apparently to inquire into the possible consequences of spinal concussion in railway injuries to man that the author conceived the idea of dropping a number of dogs from a height of twenty-four feet onto their buttocks. . . .

How far the dog's spine resembles or differs mechanically from man's is not worth the author's consideration; and how far the dropping of a dog from a height to his nates in 135 cases and on his back in six represents the kind of injury to which human beings are liable in railway concussions or smashes we leave to our readers to judge, however, the dogs were "hoppled"—whatever that may mean. It did not require these experiments to show that a dog when severely injured does not "attend to his toilet". . . . We can hardly wonder that the author was exposed to "considerable annoyance" at one time. . . ."
1. B.M.J., No. 15, 1890.

Russell reports extensive observations on "a characteristic organism of cancer".

"In conclusion it is only necessary for me to remind you that this class of fungi includes the yeast fungus, and that if the presence of this parasitic fungus in cancer is confirmed by other observers, we have found in it an organism which from its very character implies the production of a fermentation product; while the nutrition, the reproduction, and the death of the fungus cannot be conceived as occurring in the tissues without producing changes not disproportionate in magnitude to the anatomical changes present in cancer."
1. Russell; B.M.J. Dec. 13, 1890.

Frederick Mason has been treating "premature sexual desire" in a boy of five. The patient "is a fine, strong, active boy, but passionate, and occasionally so strange in manner as to suggest the question whether he is really sane". At first "I circumcised him (without Chloroform). This was only of temporary benefit while the recollection of pain was on his mind. I then had a broad belt made to buckle him round the waist when he was placed in bed. On the front are two armlets, so placed as to confine the wrists and prevent his reaching the genitals with his hands. . . . This instrument of confinement, as it is not always used, but considered as a punishment for the offence, has had some good effect; but he cannot be broken of the practice when left alone in the daytime. I have now recommended that he shall be sent to a preparatory school for little boys, where he will mix with others of his own age, and probably have his mind diverted and learn more childish games".
1. B.M.J., April 27, 1872.

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Answers to On Inspection

Questions — Page 33

FIGURE 1: Basal Cell Carcinoma.

This lesion usually occurs on the face in middle-aged persons, often above the level of the mouth, and also on the chin. It starts as a small shiny pale umbilicated nodule and extends by additional nodulation with a slowly advancing rolled pearly border laced by telangiectases. Later, it ulcerates centrally.

Other, less common, presentations are:

1. A cicatrizing type which appears as a thin irregular scar, surrounded by nodules and criss-crossed by capillaries, on the forehead and scalp.

2. A card-like type which is a waxy thickening of the skin resembling morphea (localized scleroderma).

3. A cystic type which is opalescent and contains a gelatinous fluid.

4. A tenebrant type which is very destructive, but rare.

FIGURE 2: Ossifying Periosteal Fibrosarcoma

This is the least common and least malignant bone connective tissue tumor. It occurs mainly in young adults, commonly in the femur and tibia. It originated in the periosteum but there is a medullary type which starts in the marrow cavity and grows through the cortex. It expands and osteolyses causing a concavity in the bone surface. Reactive ossification may occur and give the appearance of a Codman triangle on X-ray. Grossly, the tumour presents as a solid white firm mass with a pseudocapsule.

Treatment is by amputation, as the malignancy responds poorly to irradiation.

FIGURE 3: Cluster of Scolices of Echinococcus Granulosus.

Echinococsis is contracted by ingestion of the eggs found in canine excreta. The embryos emerge in the gastrointestinal tract, enter the mucosa and pass via veins and lymphatics to the liver and lungs particularly but also to other organs (brain, bones . . .) Here the cyst develops. It consists of two layers: an ectocyst and a germinal endocyst. The latter gives rise to the scolices which are immature heads of E. granulosus bearing hooklets and four suckers. The cycle is completed when the final host (dog, wolf, cayote) consumes meat containing the scolex-bearing cysts. These develop into the 5mm., four-segmented, hooked and suckered adults in the intestine of the host, where they discharge their ova.

Daughter cysts can arise also in the primary cyst (endogenous) or can grow from within towards the outside (exogenous).

Symptoms depend on the location and size of the cyst. e.g. pathological fractures, epilepsy, liver and pulmonary symptoms. Rupture into the pleural or peritoneal cavity may lead to acute anaphylactic shock.

The diagnosis is obtained by radiography of the calcified lesion, peripheral eosinophilia, and the Casoni skin test for sensitivity to hydatid protein.

Treatment consists of surgical excision or marsupialization of the cyst.

FIGURE 4: Herpes zoster.

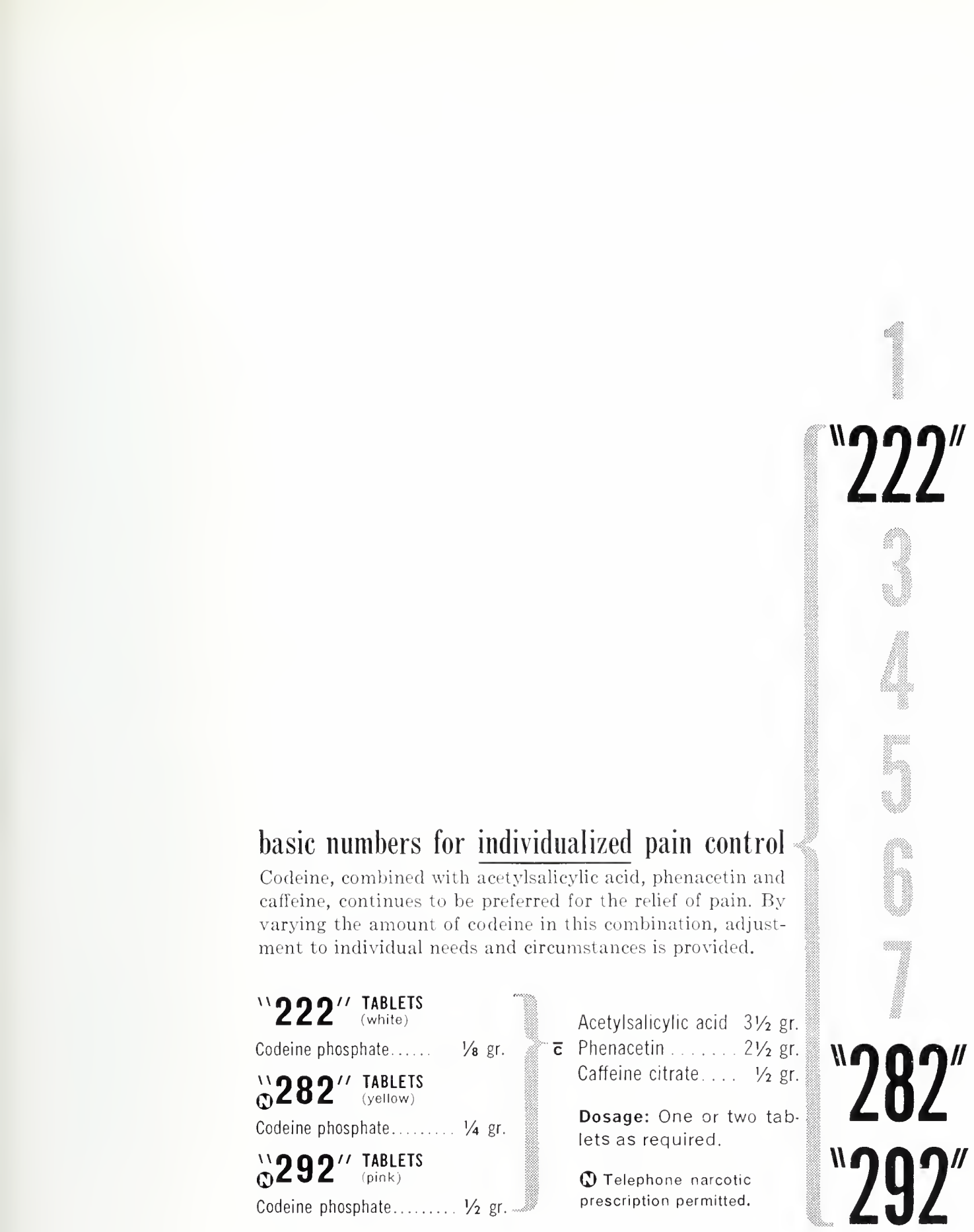
This condition is rare in children and increases in frequency and severity with age. It is more common in males. The incubation period of three weeks is followed by pre-eruptive fever and constitutional symptoms, with pain, paresthesia and hyperesthesia over the segmental distribution of the affected nerve. After three days the skin of this area becomes red and covered by papules which vesiculate on an erythematous base, either singly or in groups. Pustules form in another three days and finally crusts in about a week.

Seventy-five percent of cases are localized between segments T2 and L2, and the next most common site is the Trigeminal nerve, especially the opthalmic division. In the latter case, lesions appear in the cornea, sclera, and ciliary body.

The vesicles are usually unilateral, and painful in adults. Regional adenopaehy and secondary bacterial infection are common. The CSF may show increased pressure and a pleocytosis of up to 300.

The disease lasts two to five weeks and may be followed by postherpetic neuralgia.

Treatment is symptomatic.



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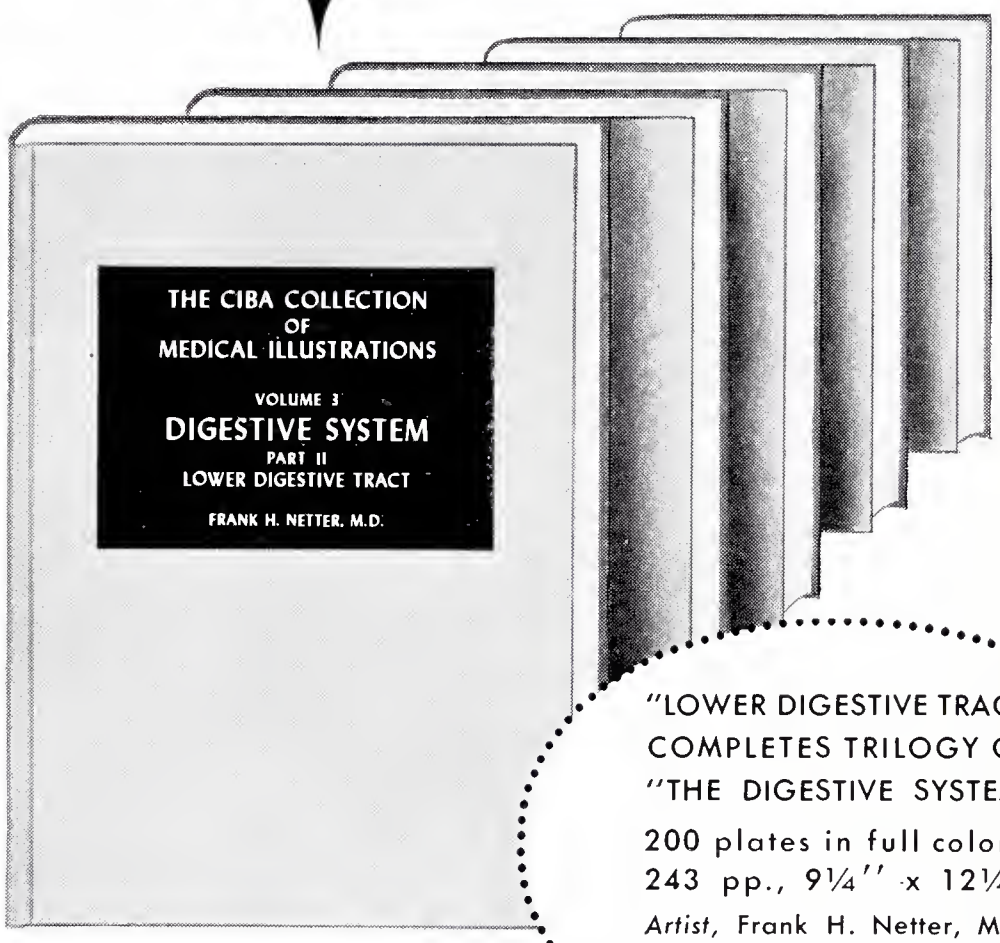

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